

BARRIERS TO UPTAKE OF GENETIC SERVICES IN FAMILIES OF PEDIATRIC HYPERTROPHIC CARDIOMYOPATHY PATIENTS

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University of Pittsburgh, 2019

ABSTRACT

Hypertrophic cardiomyopathy (HCM) is a common cardiovascular condition that is defined by unexplained left ventricular hypertrophy. A causative pathogenic variant can be detected via molecular testing in the majority of HCM cases. Pediatric HCM cases are typically predicted to be more severe than adult-onset cases and are more likely to be associated with a pathogenic variant. Barriers to genetic testing that have been established by prior studies include individual barriers such as unawareness and/or lack of knowledge regarding genetic services and institutional barriers including healthcare professionals' lack of awareness and knowledge regarding genetic services. The purpose of the study was to better elucidate the barriers to genetic testing in pediatric HCM patients and their families at UPMC Children's Hospital of Pittsburgh.

Data was collected via an anonymous survey utilizing Qualtrics software. The survey was distributed through a recruitment letter and several reminder emails that contained survey links. Of the 12 respondents, 7 (58.3%) had pursued genetic testing for their child. Of the 5 participants whose children had not received genetic testing, 4 (80%) expressed interest in pursuing it but had not for reasons including insurance denial, uncertainty regarding how to pursue it, and more pressing health concerns for their child. Lastly, this study identified deficits in respondents' understanding of GINA.

This study identified several important findings that have public health significance and can be utilized to develop a plan to address barriers to genetic testing within this patient population. To reduce the chance the genetic testing gets denied by insurance, healthcare institutions should make every effort to ensure patients receive an intake, evaluation, education, and consent by a genetic counselor. Additionally, genetic counselors can typically offer alternative finance options by working directly with the lab, to decrease the chance that cost is a barrier. Methods to address this and additional concerns regarding education and awareness within this population can be directed by the newly formed Cardiovascular Genetics Clinic at UPMC Children's Hospital of Pittsburgh.

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PREFACE

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1.0 INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a common cardiovascular condition that is estimated to affect approximately 1 in 500 adults (Maron et al., 1995). HCM is characterized by thickening of the left wall of the heart and can involve symptoms including chest pain, dyspnea, syncope/presyncope, seizures, heart palpitations, dizziness, fatigue, or malaise (Lyng et al., 2016). Often, sudden cardiac death is the first clinical presentation of HCM without any preceding cardiac symptoms (Maron et al., 1982). In about 60% of HCM cases, a causative pathogenic variant can be detected via molecular testing (Gersh et al., 2011). HCM is also a relatively common childhood cardiac condition, with an estimated incidence of 0.47/100,000 children (Lipshultz et al., 2003). Pediatric HCM is associated with increased risk for cardiac arrest (Marian, 1995), increased severity, and increased likelihood of detecting a pathogenic variant associated with the condition (Gómez et al., 2016). Despite the valuable information that genetic testing can provide for children and families affected with HCM, genetic testing is still not yet a standard of care for pediatric HCM patients. Furthermore, many of these families do not receive genetic testing. Barriers to genetic testing that have been elucidated in other studies across different genetic counseling settings include inadequate insurance coverage, unawareness, low perceived susceptibility, anxiety and distress, financial concerns, limited interest, and provider failure to refer or recommend genetic testing (Anderson et al., 2012; Delikurt et al., 2014). Additionally, one study that looked at adult HCM patients specifically found that barriers to genetic testing included distress regarding genetic test results as a reason for not pursuing genetic services (Khouzam et al., 2015).

The purpose of this study is to explore what barriers to genetic testing exist in families of pediatric HCM patients. For this study, an anonymous survey was developed utilizing Qualtrics software through a University of Pittsburgh license and distributed via a recruitment letter and reminder emails to the parents of pediatric HCM patients who have been followed by the Department of Cardiology at UPMC Children's Hospital of Pittsburgh. Inclusion criteria for this study included patients with a clinical diagnosis of non-syndromic HCM. Data were analyzed using descriptive statistics and included information from parents who pursued genetic testing for their child with HCM as well as parents who did not pursue genetic testing for their child with HCM.

The results of this study have the potential to impact the standard of care for pediatric HCM patients and their families. First, this study can help determine the barriers to genetic testing within this population. This will allow clinicians, including cardiologists and genetic counselors, to address specific issues when they meet with these families to improve accessibility and awareness of genetic testing. Additionally, this study also has the potential to elucidate information regarding attitudes and understanding regarding what genetic testing and their child's test result means for their family. While this study analyzes responses from a small sample in a specific geographic location, this survey can be applied to a larger patient population to determine if there are any statistically significant differences between families who have and have not pursued genetic testing in the measures that are assessed within this survey, including events surrounding diagnosis, family history, perceived risks and benefits of testing, and attitudes and beliefs towards genetic testing.

1.1 SPECIFIC AIMS

Specific Aim 1: Survey the parents and/or guardians of pediatric patients with HCM who have been seen by pediatric cardiology at UPMC Children's Hospital of Pittsburgh and received a clinical diagnosis of HCM. This sample will include families who have not received genetic testing for HCM as well as a comparison group of families who did pursue genetic testing. Surveying will be performed by utilizing and electronically distributing a survey instrument that will be obtained and adapted from Khouzam et al. (2015) with permission.

Specific Aim 2: Analyze the survey data to elicit the reasons parents and/or guardians do not pursue genetic testing for their children.

Specific Aim 3: Identify barriers so that strategies to reduce these barriers can be incorporated into the newly formed Cardiovascular Genetics Clinic, a collaborative effort between genetic counselors in the Division of Medical Genetics and physicians in Cardiology to increase the awareness and accessibility of genetics services to pediatric cardiology patients and their families at UPMC Children's Hospital of Pittsburgh.

2.0 LITERATURE REVIEW

2.1 HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is a common cardiovascular condition that is defined by unexplained left ventricular hypertrophy. The thickening of the left wall of the heart impairs the heart's function and efficiency in pumping blood and can potentially block blood flow out of the left ventricle. Resulting clinical manifestations may include syncope, shortness of breath, and/or sudden cardiac death; however, most individuals with HCM are asymptomatic. Other pathologic features that are associated with HCM include asymmetric left ventricular hypertrophy that widely varies with respect to extent and location, reduced left ventricular cavity dimensions, hyperdynamic systolic dysfunction, papillary muscle abnormalities, irregularities of the mitral valve, and atypical diastolic function with atrial enlargement (Klues et al., 1995). HCM can be sporadic or familial and is clinically and genetically heterogeneous, even within families. This literature review will primarily discuss familial HCM and examine the distinction between pediatric and adult HCM, as pediatric patients with HCM and their families are the focus of this study.

2.1.1 Clinical Features

The majority of individuals with hypertrophic cardiomyopathy are asymptomatic (Maron et al., 2000; Spirito et al., 1989). The most common symptoms of HCM can include chest pain, dyspnea, syncope/presyncope, and seizures; additional clinical manifestations of HCM can also

include heart palpitations, dizziness, fatigue, or malaise (Lyngé et al., 2016). In a subset of individuals, sudden cardiac death is the first clinical presentation of HCM without any preceding cardiac symptoms (Maron et al., 1982). In about 25% of HCM cases, left ventricular outflow tract obstruction (LVOTO) is present (Maron et al., 2003b). This finding in the context of an HCM diagnosis has been associated with more rapid deterioration and an increased risk for sudden cardiac death. Furthermore, LVOTO is typically managed and treated differently than non-obstructive hypertrophic cardiomyopathy (NOHCM), which will be further discussed in section 2.1.6.

A study that was conducted between 1970 and 1999 followed 225 patients for yearly intervals in order to better understand the clinical course and outcomes of HCM and evaluate risk factors that can precede sudden cardiac death. The findings of this study revealed that syncope was the only risk factor significantly associated with an increased risk of sudden cardiac death. Additionally, patients with a significant LVOTO typically resulted in decreased functional status at follow-up, while NOHCM patients tended to have a more prolonged and stable clinical course (Kofflard et al., 2003). Another study aimed to compare the LVOTO and NOHCM through analysis of the electrical activity, heart imaging studies, and clinical findings of 44 patients. Results of this study indicated that there was a greater incidence of myocardial infarction, increased interventricular septum measurement, and reduced telesystolic diameter of the left ventricle in the LVOTO compared to the NOHCM group. Conversely, there was increased supraventricular arrhythmia and reduced left ventricular hypertrophy in the NOHCM group. The study's researchers also found a higher overall prevalence of NOHCM versus LVOTO; there were no age or sex differences between the LVOTO and NOHCM groups. Additionally, in both types of

cardiomyopathy, improvement with treatment was more likely to be sustained with calcium antagonists than beta-blockers (Almenar et al., 1996).

In terms of prognosis, historical estimates of HCM mortality rates in adults ranged from 2-4% per year, which were primarily established by early retrospective studies (Kofflard et al., 1993). As management and treatment for HCM has improved over time and the research studies have become more accurate, mortality estimates for individuals with HCM have decreased across all ages. Multiple large cohort studies have been conducted recently that have established a mortality rate of 0.5% in children, adolescents, young adults, adults, and advanced age HCM patients (Maron et al., 2015; Maron et al., 2013; Maron et al., 2016).

2.1.1.1 Pediatric Clinical Features

Hypertrophic cardiomyopathy has been traditionally considered an adult-onset condition; HCM most commonly emerges during adolescence or adulthood and the average age of diagnosis is approximately 39 years old, according to the Hypertrophic Cardiomyopathy Association database (“When Does Hypertrophic Cardiomyopathy Develop?” n.d.). However, HCM is also a relatively common childhood cardiac condition that can manifest differently than in adulthood. In fact, research has indicated that pediatric HCM cases are associated with increased severity and an increased likelihood to be associated with a pathogenic variant than adult-onset HCM cases (Bales et al., 2016).

It has been historically estimated that up to 40% of children with pediatric cardiomyopathies, including HCM, progressed to death or required a heart transplant within 5 years of their initial diagnosis (Kindel et al., 2012). This can be contrasted with the results of an adult HCM study that analyzed a sample of 1259 HCM patients from three cohorts. This study found that only 3.5% of HCM patients progressed to end-stage disease with systolic dysfunction,

LV dilation, and/or LV hypertrophy; the mean age of the patients in this study was 40 years (range: 3 to 63 years) at initial evaluation (Harris et al., 2006). Furthermore, prior studies that evaluated the progression of HCM in adults estimated only up to 15% of the individuals with the condition progressed to end stage (Maron and Spirito, 1998; Spirito et al., 1987).

More recent pediatric research that directly disputes the finding that almost half of children with HCM experience significant heart disease progression. Colan et al., 2007 aimed to analyze the epidemiology and outcomes of pediatric HCM and was conducted utilizing the Pediatric Cardiomyopathy Registry (PCMR), which is a research registry that has been funded by National Heart Lung and Blood Institute and has followed more than 3500 North American children with cardiomyopathy (Wilkinson et al., 2010). The sample for this study consisted of 855 children, who were all under the age of 18. The results of the study indicated that diagnosis of idiopathic HCM carries a worse prognosis in infancy, but if an infant survives past 1 year old, then the survival rate is equivalent to survival rate at any age of diagnosis (Colan et al., 2007).

There are also historical misestimations regarding the mortality rate of pediatric HCM. Previous pediatric studies completed in the United States reported an annual mortality rate of up to 6% (Arghami et al., 2017). However, a study analyzed PCMR data that stratified specific risk factors in 1085 children with HCM and compared mortality and heart transplantation rates between groups. The results of this study indicate that children with multiple risk factors, including an underlying metabolic condition, mixed hypertrophic and dilated cardiomyopathy, or restrictive cardiomyopathy, have an increased risk for sudden cardiac death or requiring a heart transplantation (Lipshultz et al., 2013). These varied estimates in pediatric studies indicate that further research is required to elucidate a more accurate approximation of pediatric HCM mortality rates; certain subgroups may have a significantly increased risk for mortality, which is distorting

the true prognosis for a typical diagnosis of pediatric HCM (Lipshultz et al., 2013). However, whether or not the mortality rate is overestimated, affected children are at higher risk for sudden cardiac death than affected adults (Marian, 1995). In consideration of the more recent research on pediatric HCM in conjunction with the advent of more effective surgical interventions, the prognosis for pediatric HCM is better than previously reported.

2.1.2 Prevalence

Historically, the estimated prevalence of hypertrophic cardiomyopathy in adults is about 1 in 500. This estimate was based on a study that looked at echocardiographic data of 4,111 subjects ages 23-35 in the Coronary Artery Risk Development in (Young) Adults (CARDIA) sample that took place between 1987 and 1988 (Maron et al., 1995). However, with the rise of genetic testing, detection of pathogenic variants in the general population, and identification of more at-risk and affected individuals, recent data indicate that the estimate for HCM prevalence is as high as about 1 in 200 (Semsarian et al., 2015).

2.1.3 Diagnosis

Familial HCM can be diagnosed clinically and by molecular testing. However, HCM often has multiple cardiac and/or genetic differential diagnoses that should be considered during evaluation. Heart conditions that can mimic the features of familial HCM include acquired left ventricular hypertrophy, cardiac amyloidosis, and *PRKAG2*-associated disorders; HCM in these conditions may be transient or secondary to an underlying accumulation of amyloid protein or glycogen, respectively (Cirino and Ho, 2008).

There are also possible underlying genetic, metabolic, and neuromuscular conditions that are associated with HCM. These are typically distinguished from familial, idiopathic HCM by the presence of additional symptoms, which may be harder to discern in a pediatric population. Some genetic conditions that should be ruled out in the context of HCM include Fabry disease, Danon disease, Pompe disease, mitochondrial disease, Noonan syndrome, and Friedrich ataxia (Cirino and Ho, 2008). One study that looked at 855 children affected with HCM found that 25.2% had an underlying metabolic, neuromuscular, or malformation condition; the remainder were diagnosed with idiopathic HCM (Colan et al., 2007). This study underlines the importance of evaluating HCM patients for potential differential diagnoses, especially in a pediatric setting.

2.1.3.1 Clinical Testing

HCM is typically clinically diagnosed utilizing non-invasive cardiac imaging technologies, including an echocardiogram or cardiac magnetic resonance imaging. Clinical diagnostic criteria for HCM state that heart wall thickness must be increased to 1.5 cm or greater in adults (Maron et al., 2003a). In children, a diagnosis can be made for an increased heart wall thickness equivalent to that in an adult relative to body surface area (Gersh et al., 2011).

2.1.3.2 Molecular Testing

Molecular testing can provide a genetic diagnosis of HCM for individuals who may or may not clinically present with the condition. The genes that are most frequently associated with familial HCM are *MYH7* and *MYBPC3*, which each account for about 40% of pathogenic variants that are associated with HCM (Hershberger et al., 2018; Cirino and Ho, 2008). Additional HCM-associated core genes, as established by the Heart Failure Society of America in collaboration with the American College of Medical Genetics and Genomics, include *TNNT2*, *TNNC1*, *TNNI3*,

TPM1, MYL2, MYL3, ACTC1, ACTN2, CSRP3, PLN, TTR, PRKAG2, LAMP2, and GLA (Hershberger et al 2018).

Pre-conception and prenatal testing for HCM is becoming increasingly more common, as genetic testing for HCM is becoming more widespread and additional genetic causes of HCM are being identified. Pre-implantation genetic diagnosis (PGD) for inherited cardiac diseases has been researched and successfully completed in multiple couples. One specific study described 18 PGD cycles undergone by patients who had a genetic predisposition for a cardiac disease; three patients in the study carried a pathogenic variant associated with HCM. The outcomes of this study included the births of seven children that did not carry a disease-causing or disease-predisposing pathogenic variant. However, no successful births occurred for the patients with an HCM-associated pathogenic variant. This study did not explore the motivations of the families who underwent PGD testing for familial HCM. However, this paper alludes to the fact that while certain inherited cardiac disease may be milder, the initial presentation could potentially be premature death which warrants offering the option of PGD to those families (Kuliev et al., 2012).

2.1.4 Molecular Genetics

HCM is considered the most common inherited cardiac disease (Maron et al., 2014). In about 60% of HCM cases, a causative pathogenic variant can be detected via molecular testing (Gersh et al., 2011). The majority of genetic changes interfere with the function of the sarcomere (Ho and Seidman, 2006). The sarcomere is the basic unit of muscle structure; sarcomeres are contractile regions in the myofilament structure composed of actin and myosin. In addition to HCM, sarcomere dysfunction has also been implicated in heart failure and other familial heart conditions such as dilated cardiomyopathy (DCM) (Hamdani et al., 2008; Lakdawala et al., 2010).

There is significant genetic heterogeneity present in HCM. In fact, most pathogenic variants that are associated with familial HCM are specific to an individual family and are unlikely to be detected in unrelated individuals (Ho, 2013). An OMIM search of ‘hypertrophic cardiomyopathy’ yields 1,035 results (“OMIM Entry Search,” 2018). A ClinVar search of ‘hypertrophic cardiomyopathy’ yields 6383 results (“ClinVar Entry Search,” 2018b). It is important to note that HCM is a feature of several genetic conditions, which was discussed in section 2.1.3; thus, these conditions are included in the search results in addition to familial, idiopathic HCM. When ‘familial hypertrophic cardiomyopathy’ was searched in ClinVar, this yielded 3326 results. Of these variants, only 523 are classified as ‘pathogenic,’ while 2,001 are classified as ‘uncertain significance’ (“ClinVar Entry Search,” 2018a). The large number of variants that have been identified and suggested to potentially be associated with HCM underscores the clinical utility of larger-scale genetic testing, including panel and exome testing; this will further detect and clarify variants associated with HCM, which will ultimately lead to cascade screening and identification of at-risk family members.

There are also potential drawbacks of larger-scale genetic testing within the context of HCM, given there are almost four times the number of variants of uncertain significance suggested to be associated with HCM compared to known pathogenic variants. One study conducted by Gómez et al. (2016) found that an estimated 11% of patients with HCM who receive genetic testing are found to have rare variants unique to his or her family. Furthermore, it is unlikely that all of these variants are pathogenic and may be benign genetic changes unrelated to an HCM diagnosis. However, given the rarity of these variants and the fact that many will unlikely be found in other families, laboratories’ abilities to gather more information regarding these rare genetic changes are limited. This study also indicated that the likelihood of finding a pathogenic variant is increased

when patients have severe early-onset HCM and/or a related family history (Gómez et al., 2016). Given the potential for uncertainty, especially in HCM patients with a milder phenotype, advanced age of onset, and no family history, informed consent is imperative for families interested in pursuing genetic evaluation.

2.1.4.1 Factors Associated with Familial HCM

One study was conducted to analyze the clinical predictors of genetic testing outcomes in HCM. This research took place over a 10-year period; 265 unrelated probands were studied. Of these individuals, 138 probands (52%) tested positive for at least one pathogenic variant causative of HCM. The results of this study also indicated via multivariate analysis that female sex, increased left ventricular wall thickness, a family history of HCM and/or sudden cardiac death were the clinical factors associated with the greatest chance of identifying a pathogenic variant (Ingles et al., 2013).

While family history is a valuable clinical tool in increasing the detection rate of pathogenic variants, isolated HCM cases may still have an underlying genetic basis. Another study provided genetic testing to 57 individuals with either an HCM or DCM diagnosis. Of the individuals tested, 70% received positive genetic testing for a pathogenic variant. Of the probands with a positive result, almost half (40%) reported no family history of cardiomyopathy at their initial evaluation (Miller et al., 2013). As previously discussed, the first symptom of HCM is often sudden cardiac death. While a “negative” family history may indicate that close relatives of the proband were not formally diagnosed with HCM, there may be clinical indications including non-specific symptoms or causes of death that may suggest relatives were affected but undiagnosed. Thus, genetic testing is important to offer to all HCM patients, even in the context of a “negative” family history.

2.1.4.2 Genotype-Phenotype Correlation

Familial HCM has a number of genotype-phenotype correlations, of which a select few will be highlighted in this section. The aforementioned study by Ingles et al. (2013) also analyzed genotype-phenotype correlation in carriers of pathogenic variants associated with HCM. Individuals in this study who carried a pathogenic variant in *TNNT2* received an earlier diagnosis, while carriers of pathogenic variants in the *TNNI3* gene had an increased likelihood of an out-of-hospital cardiac arrest or sudden cardiac death. Additionally, individuals in this study who carried a pathogenic variant in *MYH7* presented clinically and were diagnosed at significantly younger ages than carriers of an *MYBPC3* pathogenic variant. In addition, a research study conducted by Viswanathan et al. (2017) showed that the HCM phenotype that arose from pathogenic variants in *MYBPC3* is indistinguishable from an *MYH7* HCM phenotype.

Genotype-phenotype correlation has also been researched with respect to carriers of multiple genetic changes in genes that are associated with HCM. About 6% of patients with HCM have been reported to carry 2 or more sarcomere variants. Carriers of multiple pathogenic variants were more likely to have an out-of-hospital cardiac arrest or sudden cardiac death than carriers of a single pathogenic variants (Ingles et al., 2013). Other characteristics of individuals who carry multiple pathogenic variants causative of HCM also can include more significant left ventricular hypertrophy, earlier age at diagnosis, and treatment with invasive surgical intervention (Ingles et al., 2005). Additionally, some pathogenic variants that are causative of HCM have also been

Currently, there is limited clinical utility in using genotypic information to predict risks and guide management. However, further research on genotype-phenotype correlation in familial HCM could lead to the development of risk-stratification algorithms that can predict clinical outcomes

to guide management based on the number of pathogenic variants a patient has, in which genes they are located, and the specific pathogenic variant(s) identified.

2.1.5 Inheritance

Familial HCM is inherited in an autosomal dominant manner. If an individual is identified to have a pathogenic variant that is causative of HCM, there is a 50% risk that he or she will pass the pathogenic variant to each future child. The de novo mutation rate in patients with HCM is estimated to be about 30% (Konno et al., 2010).

HCM, like other inherited cardiac disease, has variable expressivity and incomplete, age-dependent penetrance. A study conducted by Jensen et al. (2013) that examined 90 probands and 361 relatives who underwent clinical screening and/or genetic testing and found that only 6% of at-risk relatives of probands were identified to have HCM during childhood or early adulthood, suggesting a low penetrance rate.

2.1.6 Management

There are several management and treatment options for both children and adults who have been diagnosed with HCM. The recommendations of these options depend on severity of disease, age-of-onset, and family history. Typically, these management guidelines and treatment options are available for both children and adults, unless indicated otherwise. While there is no cure for HCM, there are ways to manage and treat symptoms of the condition as well as reduce the risk for sudden cardiac death.

2.1.6.1 Surveillance

Individuals who are diagnosed with HCM are recommended to follow-up for clinical, echocardiographic, and electrocardiographic evaluation every 12-18 months following initial diagnosis (Maron et al., 2003a). With respect to the management of family members, current guidelines recommend that all first-degree relatives of individuals with HCM are clinically evaluated via 12-lead ECG and annually imaged for children beginning around age 10-12 years until age 18-21 years, and every 2-5 years in adults (Elliott et al., 2014). Lifestyle changes, pharmaceutical therapy, and prophylactic surgical intervention are not indicated for at-risk individuals until cardiac evaluations indicate a clinical diagnosis of HCM.

2.1.6.2 Lifestyle Changes

Lifestyle changes in individuals with HCM are typically the first management recommendation made for individuals with HCM, even before pharmaceutical therapy, in the context of an asymptomatic patient with a milder form of disease (Michels et al., 2017). The most common lifestyle change for individuals with HCM is limitation of physical activity. It is recommended that individuals with HCM do not play competitive sports of any kind. Any high-intensity exercise or competitive physical activity that may involve impact puts an individual with HCM at higher risk for sudden cardiac death. However, low-impact, noncompetitive physical activity is encouraged for individuals with HCM. This may include some low-intensity weight lifting, recreational golf, or some light cardio (e.g., walking or running) (Elliott et al., 2014).

2.1.6.3 Pharmaceutical Therapy

Pharmaceutical management historically has been the first-line treatment option for patients with HCM. Prior to the introduction of more invasive preventative measures of sudden

cardiac death, pharmaceutical therapy was historically utilized to prevent sudden cardiac death in patients with HCM. However, it has been more recently established that medications are not effective in preventing sudden cardiac death (Melacini et al., 2007).

While pharmacological treatments do not prevent sudden cardiac death, research has shown that medications can alleviate symptoms and improve the clinical course of HCM. One study that looked at both LVOTO and NOHCM found that calcium-antagonists were more likely than β -blockers to demonstrate an improved, prolonged clinical course in both groups (Almenar et al., 1996). The recommended progression of drug therapy in individuals with OCHM is to treat initially with β -blockers; if those are ineffective and/or contraindicated, disopyramide and verapamil are considered second-line drug therapy options (Elliott et al., 2014).

2.1.6.4 Surgical Intervention

Surgical intervention is another recommended management approach for HCM, typically for individuals for whom medications have been attempted, individuals with severe symptoms, and/or individuals with LVOTO. In fact, the therapeutic gold standard for individuals with LVOTO and severe symptoms is a surgical myectomy, also known as a septal myectomy (Sorajja et al., 2009). This was established by a study that explored the long-term survival of individuals with HCM with LVOTO who received a surgical myectomy. This study's sample consisted of 1,337 HCM patients who were followed for an average of 6 years. Researchers compared total and HCM-related deaths between three subgroups: HCM patients with LVOTO who received a surgical myectomy, HCM patients with LVOTO who did not receive a surgical myectomy, and HCM patients without obstruction. The results of the study indicated that the survival rates in HCM patients with LVOTO who received surgical myectomy are comparable to age- and gender-matched unaffected individuals in the general population as well as HCM patients without

obstruction. Additionally, HCM patients with LVOTO who received surgical myectomy had significantly higher survival rates when compared to HCM patients with LVOTO who did not receive surgical myectomy (Ommen et al., 2005). This study highlights the significantly improved outcomes for severely affected individuals that pursue this surgical option. To explore this surgical approach for other HCM populations, another study aimed to determine whether or not prophylactic surgical myectomy would be an appropriate treatment option for individuals without LVOTO. The results of this study indicated that mildly symptomatic or asymptomatic patients had only a slightly increased mortality rate over the general population and thus would likely not benefit from this treatment option (Sorajja et al., 2009). An alternative to this procedure is septal alcohol ablation, which has similar outcomes in functional status improvement and comparable procedural mortality risks when compared to surgical myectomy. However, septal alcohol ablation carries an increased risk for AV block (Elliott et al., 2014).

Another means of treatment for LVOTO is internal cardioverter defibrillator (ICD) implantation. Consideration of ICD implantation is recommended for patients who are considered moderate and high risk for sudden cardiac death (Elliott et al., 2014). This may be based on cardiac imaging, history of a documented abnormal heart rhythm, and/or family history of sudden cardiac death. ICD has been established as a highly effective treatment option in preventing sudden cardiac death. A study followed 16 HCM patients, all of whom were successfully screened, for a median 17.5 months after they had ICDs placed. During this follow-up period, no appropriate shocks were required or administered in this cohort. However, one inappropriate shock was received by one individual during the follow-up period. No sudden cardiac deaths were noted (Weinstock et al., 2016).

2.1.7 Genetic Screening Guidelines

Current recommendations for screening in patients and families with HCM include genetic testing beginning with an affected family member, cascade screening for family members of individuals who have received a pathogenic or likely pathogenic genetic test result, and consideration of genetic testing for evaluation of HCM in infants (Hershberger et al., 2018).

A recent study looked at the impact of genetic testing in probands and cascade screening in relatives. The study population consisted of 777 relatives of 209 unrelated probands, who had been evaluated for HCM between 1985 and 2016. A pathogenic variant that explained their HCM was found in 72% of these probands, and 80% of the total relatives pursued genetic testing. Almost half (43%) of the relatives tested positive for the known familial pathogenic variant. Another significant result of this study was that 46% of the relatives in the study were discharged from clinical follow-up based on their negative genetic test result (van Velzen et al., 2018). This study findings highlight the importance of genetic screening in conjunction with clinical evaluation in identifying family members of probands at-risk for HCM, as well as the value of genetic testing to prevent unnecessary clinical screening in family members who are not at risk.

2.1.8 Impact of Genetic Evaluation

Traditionally, individuals with HCM have been evaluated, diagnosed, and managed clinically. Today, research has established that HCM is an inherited condition that often has an underlying genetic basis. Both clinical and genetic evaluations of HCM can provide more detailed information regarding severity, management, inheritance, and prognosis than just clinical and/or genetic evaluation alone (Ho, 2010).

It has been proposed that incorporating genetic testing into the management of families with HCM creates a more cost-effective approach model than traditional clinical follow-up of at-risk family members. As previously discussed, traditional surveillance recommendations for first-degree relatives of an individual with HCM include regular cardiac screening and evaluation. Conversely, when a proband receives genetic testing and tests positive for a pathogenic variant causative for HCM, cascade screening of other family members can occur. This has the potential to identify family members who do not carry the known familial variant causative of the HCM in the family and who will no longer need regular cardiac evaluations and follow-up. Additionally, multiple studies have established genetic testing as a more cost-effective model in the evaluation of HCM patients and their family members when compared to traditional clinical management and screening methods (Ingles et al., 2012; Wordsworth et al., 2010). A study conducted by Ingles et al. (2012) aimed to analyze the cost difference via probabilistic mathematical modeling between incorporating genetic testing into management of Australian families with HCM compared to clinical follow-up without genetic testing. This study found that the proposed genetic testing strategy resulted in increases in quality-adjusted life years and life-years gained as well as resulted in a projected decrease in cost of proband testing; thus, this model would be highly cost-effective. The benefits of genetic testing in the diagnosis and management of HCM introduces the question of why some families with HCM do not pursue genetic services and/or genetic testing.

2.2 BARRIERS TO GENETIC SERVICES

2.2.1 Definition

Barriers to genetic services can be defined as the actual or perceived motivations that result in individuals with a genetic risk choosing (either knowingly or unknowingly) not to pursue genetic testing. Barriers that have been elucidated in previous studies include inadequate insurance coverage, unawareness, low perceived susceptibility, anxiety and distress, financial concerns, limited interest, and provider failure to refer or recommend genetic testing.

The majority of research on the barriers to genetic services and testing was conducted within cancer genetic services. However, this research is informative for other genetic counseling settings, especially prior to the study of barriers within these settings. One study offered genetic counseling services to 97 women who were between the ages of 30 and 60 years with a family history of breast cancer. This study was unique because researchers offered free genetic counseling sessions, which removed cost as a potential barrier to genetic services. Fifty of the women accepted the offer of genetic counseling. Factors associated with individuals who were more likely to undergo genetic testing included increased perceived susceptibility to breast cancer and carrying a *BRCA1* or *BRCA2* pathogenic variant, as well as a higher education level. Of the 47 women who did not pursue genetic counseling, disinterest, not wanting to discuss breast cancer, not having enough time, experiencing unrelated health problems, and low perceived susceptibility to breast cancer were reasons to decline the service reported by 26 participants (Culver et al., 2001). Similarly, another study that looked at a population of women who were diagnosed with breast cancer before age 50 from 2006-2007 found that the most common reasons that were cited by

women who did not pursue genetic testing were lack of provider recommendation/referral and concerns regarding insurance coverage (Anderson et al., 2012).

Delikurt et al. (2014) conducted a systematic review that analyzed the barriers to patient referral to genetic services based on the findings of nine articles. This paper differentiated the most frequently reported factors that are associated with underutilization of genetic services into two categories: barriers related to individuals and barriers related to healthcare professionals. Individual barriers included unawareness and/or lack of knowledge regarding personal risk, family member risk, and genetic services. Barriers related to healthcare professionals included lack of awareness and knowledge regarding patient risk factors and genetic conditions and services, not obtaining a complete family history, not properly coordinating or providing referral, or lack of genetics workforce. This systematic review identified findings delineated in the two aforementioned studies, which all indicate that the barriers to genetic testing primarily lie within the awareness and knowledge of the patient and their healthcare provider.

2.2.2 Pediatric Genetic Services

Barriers to genetic testing in pediatric populations have been analyzed for various conditions, as genetic testing for pediatric conditions has become more prevalent. For example, one study looked at the reasons that genetic testing was not pursued as frequently as expected in families with children who have an autism diagnosis. The researchers received 155 unique survey responses for this study and found that the major factors that affected families pursuing genetic testing included failure of provider to recommend testing, parental unawareness, parental disinterest, and inadequate insurance coverage. It was also found that families who pursued genetic testing were more likely to ask for a referral to genetics and/or more likely to have primary care

providers who suggested genetic services. Additional factors that were associated with families who did not pursue genetic testing in this study included low parental anxiety and distress (Vande Wydeven et al., 2012).

Another study that looked at the barriers to genetic testing in the context of pediatrics specifically aimed to analyze the barriers to genetic testing in a population of children with public insurance, or Medicaid. This study was unique because researchers analyzed survey responses that were elicited from 302 healthcare providers (from a population of 1982 healthcare providers), which was primarily composed of neurologists (82%) but also represented resident physicians, nurses, and nurse practitioners. Barriers that were cited from the healthcare provider perspective included cost, provider understanding and expertise, commercial laboratories, healthcare institution, specific insurance company and coverage, and patient attitudes. These reasons were further explored through a qualitative research component of the study. For example, cost subthemes cited by respondents included that testing is too expensive, and cost outweighs benefit for their patients. Providers also discussed that they were limited in their ability to offer genetic testing, as they did not fully understand the value of genetic testing, did not know how to complete the paperwork required, and did not have enough time in appointments to fully consent patients. In terms of commercial laboratories, healthcare providers cited that labs offer too many options, and providers did not know the most appropriate test to order for their patient. In regard to healthcare institutions, providers noted that insufficient staffing as well as stricter institutional policies (e.g., requiring patients to see a genetic counselor to move forward with testing) are also significant barriers to genetic testing. Respondents discussed that insurance companies have denied testing for patients and that families cannot afford the out-of-pocket cost for testing. Lastly, patient attitudes, specifically regarding privacy and fears of misuse of their genetic information,

was another specific barrier cited by respondents (Kutscher et al., 2017). This research is important because it elicited healthcare providers' perceptions of barriers to genetic testing, which provides more information underlying the reasons that healthcare providers themselves either do not or cannot provide genetic services and/or genetic testing.

Barriers to pediatric genetic testing concerns that were emphasized throughout both parent and provider studies include financial considerations, such as parental financial concerns as well as concerns regarding insurance coverage, insurance providers, and billing issues (Vande Wydeven et al., 2012; Kutscher et al., 2017). Another factor that was emphasized in regard to barriers in pediatric genetic services is the child's primary care provider's and/or other specialty doctor's knowledge and comfort of coordinating, referring, and ordering genetic services and genetic testing, particularly in clinics without genetic professionals (Vande Wydeven et al., 2012; Kutscher et al., 2017). These specific barriers are of particular relevance to specialty clinics that provide services for children with conditions that may have a genetic etiology, but do not have access to genetic professionals (e.g., neurology and cardiology).

2.2.3 Cardiovascular Genetic Services

Barriers to genetic testing in patients seeking genetic counseling for specific cardiovascular conditions have been identified by several studies. A study that investigated barriers to genetic testing in 306 patients with HCM and their family members found that individuals who had genetic testing were more likely to have seen a genetic professional, have a family history of HCM, and have a known familial pathogenic variant that is associated with HCM. Additionally, this study revealed that individuals with HCM and their families cited distress regarding genetic test results as a reason for not pursuing genetic services (Khouzam et al., 2015).

Because insurance coverage has been cited as a barrier to genetic testing in both general and cardiovascular genetics services specifically, research has been performed that analyzed the issues in accessibility and cost associated with cardiovascular genetic testing. This research indicates that there are multiple challenges within the US healthcare system, from insurance policies to commercial laboratory billing practices to healthcare provider knowledge. For example, insurance policies often exclude cardiovascular genetic testing from coverage, citing it as “experimental,” or stating it will not change an affected patient’s medical management. Additionally, guidelines for cardiovascular genetic testing are updated infrequently and are not specific, compared to cancer genetic screening guidelines, which may be another factor contributing to insurance companies’ decision not to cover testing. Lastly, clinician unawareness of commercial laboratory policies, which typically include payment plans and cost reductions whenever genetic testing is billed directly to the laboratory rather than the institution, could result in a large out-of-pocket cost for the patient and even legal liability for the healthcare provider (Spoonamore and Johnson, 2016).

2.2.3.1 Psychosocial Factors

Psychosocial factors associated with inherited cardiovascular diseases may contribute to barriers to genetic testing in this specific population. A study conducted by Hidayatallah et al. (2014) aimed to elucidate psychosocial factors specific to families with inherited cardiovascular conditions by interviewing 50 participants from 32 families who were either being followed for a cardiogenetic condition, were parents of children who had predispositions to arrhythmias and sudden cardiac death or were families of children who passed away from explained causes. The theme that was most frequently cited by participants was guilt (N=33). These participants also

expressed recurring ideas including bereavement (e.g., numbness, disbelief), reactive anxiety (e.g., guilt, fear), and positive outcomes (e.g., closure, gratitude) regarding their experiences.

A systematic review outlined the recommendations for genetic counseling and testing for individuals with inherited cardiovascular disease by summarizing the potential positive and negative psychological impacts and modifiers for affected adults, unaffected at-risk adults, and unaffected at-risk children. This review is important because it addresses psychosocial issues unique to children, which is a perspective that is lacking in other research studies on this topic. Potential negative impacts of genetic testing in children at-risk for an inherited cardiovascular condition include frustration regarding stigmatization (genotype positive), altered self-esteem, distress over the testing process and outcome, modification of identity regarding professional aspirations and hobbies, survivor guilt (genotype negative), and the removal of some autonomy by the parent pursuing the testing. Potential positive impacts of genetic testing for children include the elimination of uncertainty, empowerment, permitting an adjustment period to a diagnosis (genotype positive), and providing relief (genotype negative). Modifiers associated with more positive impacts are positive parental attitudes, higher socioeconomic status and education level, reduced disease severity, good prognosis, and low rate of cardiac death in the family history (Aatre and Day, 2011).

Another qualitative study has identified additional psychosocial and ethical implications that may act as barriers to genetic testing. Ormondroyd et al. (2013) interviewed 22 individuals who have a clinical and/or genetic diagnosis of HCM or Long QT Syndrome (LQTS) and found that probands often failed to communicate with at-risk family members, since they did not understand the value of genetic testing. Furthermore, asymptomatic individuals viewed their risk as low, even when they were genotype positive. These potential psychosocial barriers may lead to

the increased unawareness regarding genetic testing in cardiovascular conditions among family members of affected individuals as well the general population. Challenges in communication or understanding can occur at many stages throughout the genetic testing process. For example, there may have been a failure of the healthcare provider to accurately relay the impact of the genetic test result to the patient. Additionally, patient misunderstanding could still occur even if the healthcare provider provided an accurate explanation, which could stem from reasons including low health literacy, limited knowledge regarding genetics, or even denial over a clinical and/or genetic diagnosis. This study also explored parents' reasons for pursuing or not pursuing genetic testing for their children. Parents cited not wanting to cause their child worry or negatively impacting their life through the stigmatization of a genetic diagnosis and potential limitation of physical activity as reasons for not pursuing genetic testing. Interestingly, this study also looked at quality-of-life scores for children diagnosed with inherited cardiovascular condition and found that they were not significantly different than their peers without a diagnosis. Overall, unawareness and misunderstanding of the utility of genetic testing as well as parental attitudes in the case of pediatric genetic testing may serve as potential explanations regarding why individuals who are at-risk with a family history are not pursuing genetic services.

The distinct barriers to cardiovascular genetic testing including unique psychosocial concerns associated with carrying a genetic change that can cause sudden cardiac death, inaccurate perception of risk due to the asymptomatic nature of most cardiovascular conditions, and the exclusion of coverage by insurance companies for cardiovascular genetic testing demonstrates the need for further research to be performed regarding the access and awareness of cardiovascular genetic testing for patients and their families.

3.0 MANUSCRIPT

3.1 BACKGROUND

Hypertrophic cardiomyopathy (HCM) is a common cardiovascular condition that is characterized by thickening of the left wall of the heart. HCM commonly involves symptoms such as chest pain, dyspnea, syncope/presyncope, and seizures; additional clinical manifestations of HCM can include heart palpitations, dizziness, fatigue, or malaise (Lynge et al., 2016). Often, sudden cardiac death is the first presenting feature of HCM without any preceding cardiac symptoms (Maron et al., 1982). HCM can be diagnosed clinically utilizing non-invasive cardiac imaging technologies, including an echocardiogram or cardiac magnetic resonance imaging. Individuals diagnosed with HCM are recommended to have clinical, echocardiographic, and electrocardiographic evaluation every 12-18 months following an initial diagnosis (Maron et al., 2003a). Lifestyle changes, pharmaceutical therapy, and prophylactic surgical intervention are all potential management and treatment options for individuals with HCM, depending on the symptoms a patient is exhibiting as well as disease severity and progression.

It is estimated that HCM affects approximately 1 in 500 adults (Maron et al., 1995) and is the most common inherited cardiac disease (Maron et al., 2014). In addition to traditional clinical diagnostic testing and follow-up, HCM can also be diagnosed through genetic testing. In fact, in about 60% of HCM cases, a causative pathogenic variant can be detected via molecular testing (Gersh et al., 2011). The genes that are most frequently associated with familial HCM are *MYH7* and *MYBPC3*, which each account for about 40% of pathogenic variants that are associated with HCM (Hershberger et al., 2018; Cirino and Ho, 2008). Additional HCM-associated core genes, as

established by the Heart Failure Society of America in collaboration with the American College of Medical Genetics and Genomics, include *TNNT2*, *TNNC1*, *TNNI3*, *TPMI*, *MYL2*, *MYL3*, *ACTC1*, *ACTN2*, *CSRP3*, *PLN*, *TTR*, *PRKAG2*, *LAMP2*, and *GLA* (Hershberger et al., 2018). The majority of genetic changes interfere with the function of the sarcomere (Ho and Seidman, 2006). Genetic diagnosis has the potential to determine an underlying hereditary predisposition that can explain a patient's clinical HCM diagnosis, rule out potential syndromic causes of HCM, and identify at-risk individuals (e.g., unaffected relatives of an individual with HCM) who do not have a clinical presentation of HCM but have a high risk to develop the condition based on a positive genetic test result. Current recommendations for screening in patients and families with HCM include genetic testing beginning with an affected family member, cascade screening for family members of individuals who have received a pathogenic or likely pathogenic genetic test result, and consideration of genetic testing for evaluation of HCM in at-risk infants (Hershberger et al., 2018).

3.1.1 Impact of Genetic Testing

Finding a pathogenic variant that is causative of HCM in an affected proband allows for at-risk family members to be evaluated and have appropriate management and follow-up, depending on their genetic status. In fact, research has shown that genetic testing in unaffected relatives has the potential to discharge nearly 50% of individuals being regularly followed due to a family history of HCM based on a negative genetic test result (van Velzen et al., 2018). Thus, genetic testing not only alleviates the burden of unnecessary clinical follow-up of unaffected family members, but several studies have shown that genetic screening for family members of an affected proband found to have a pathogenic variant is more cost-effective for institutions and

insurance companies compared to traditional clinical screening and follow-up (Ingles et al., 2012; Wordsworth et al., 2010). While clear benefits of genetic testing and cascade screening exist for an inherited cardiac condition, a risk of genetic testing for HCM is uncertain results and negative psychological impacts of testing. At this time, there are almost four times the number of variants of uncertain significance suggested to be associated with HCM compared to known pathogenic variants (ClinVar, 2018). However, certain clinical factors are associated with a greater chance of identifying a pathogenic variant, including increased severity of disease, female sex, increased left ventricular wall thickness, a family history of HCM and/or sudden cardiac death (Ingles et al., 2013; Gómez et al., 2016). In addition to the potential for uncertainty, research has identified psychosocial issues such as low-perceived risk, which can impact a patient's ability to fully understand their genetic test result and accurately communicate that information to at-risk family members (Ormondroyd et al., 2013). Additional psychosocial concerns associated with a positive genetic test result, especially in asymptomatic patients, include stigmatization related to a genetic diagnosis, the potential impact of a positive genetic test result on self-image, and the mental/emotional toll of physical activity restriction. (Aatre and Day, 2011). The fact that many families with HCM do not receive genetic testing for this condition, especially in the context of documented benefits and risks, suggests that further research into the barriers for families with HCM to receive genetic services is warranted.

3.1.2 Barriers to Genetic Testing

Research has identified barriers for patients pursuing genetic testing in several types of genetic counseling practice settings. The bulk of this research is focused in cancer genetic counseling, but these results have the potential to be informative for other genetic counseling

specialties. These studies established patient-specific barriers including unawareness and/or lack of knowledge regarding personal risk, family member risk, and genetic services. Additionally, barriers related to healthcare professionals were also corroborated by multiple studies, including lack of awareness and knowledge regarding patient risk factors and genetic conditions and services, not obtaining a complete family history, not properly coordinating or providing referral, or lack of genetics workforce (Culver et al., 2001; Anderson et al., 2012; Delikurt et al., 2014). Findings from studies examining barriers in both pediatric and cardiovascular genetics practices were consistent with this prior research as well. Barriers to pediatric genetic testing concerns that were emphasized throughout both parent and provider studies include financial considerations, such as parental financial concerns as well as concerns regarding insurance coverage, insurance providers, and billing issues. Furthermore, families who pursued genetic testing were more likely to ask for a referral to genetics and/or more likely to have primary care providers who suggested genetic services. Additional factors that were associated with families who did not pursue genetic testing included low parental anxiety and distress (Vande Wydeven et al., 2012). Other barriers identified in pediatric genetic services is the child's primary care provider's and/or other specialty doctor's knowledge and comfort of coordinating, referring, and ordering genetic services and genetic testing. Barriers that were cited from the healthcare provider prospective included cost, provider understanding and expertise, commercial laboratories, healthcare institution, specific insurance company and coverage, and patient attitudes (Kutscher et al., 2017). Research has been performed that identified and analyzed the issues in accessibility and cost associated with cardiovascular genetic testing. One finding was the exclusion by insurance policies of cardiovascular genetic testing from coverage, citing it as "experimental," or stating it will not change an affected patient's medical management. Additionally, guidelines for cardiovascular

genetic testing are updated infrequently and are not specific, compared to cancer genetic screening guidelines, which may be another factor contributing to insurance companies' decision not to cover testing. Lastly, clinician unawareness of commercial laboratory policies, which typically include payment plans and cost reductions whenever genetic testing is billed directly to the laboratory rather than the institution, may result in a large out-of-pocket cost for the patient and even legal liability for the healthcare provider (Spoonamore and Johnson, 2016).

Research investigating facilitators and barriers to genetic testing in an HCM population, specifically, has been limited. Facilitators to genetic testing in adult HCM patients include meeting with a genetics professional, having a family history of HCM, and having a known familial pathogenic variant that is associated with HCM. Barriers to genetic testing in this population include distress regarding genetic test results as a reason for not pursuing genetic services (Khouzam et al., 2015). There is a paucity of research examining the barriers that exist for pediatric patients with HCM. Pediatric HCM cases are associated with increased severity and an increased likelihood to be associated with a pathogenic variant when compared to adult-onset HCM cases (Bales et al., 2016). Therefore, the clinical utility of testing pediatric patients may be increased due to a higher yield and a lower risk for uncertainty. Despite the benefits and potential positive impact that exists for genetic testing in this population, many families do not pursue genetic testing or obtain genetic services, including genetic counseling. This disparity merits additional research to explore the barriers that prevent these patients and their families from obtaining genetic services and genetic testing.

3.1.3 Study Goals

This study aimed to gather data on the barriers to uptake of genetic services for pediatric HCM patients by surveying parents of affected children who pursued genetic testing and parents of affected children who did not pursue genetic testing. To our knowledge, this is the first study that looks specifically at barriers to genetic testing in a pediatric HCM population and can provide important preliminary evidence for the reasons that some families have genetic testing while others do not. Demographic information, risk factors, reasons for genetic testing decisions, and attitudes towards genetic testing were elicited and assessed to better understand the motivators and barriers for genetic testing for these families. The results of the study have the potential to impact the way providers address the topic of genetic testing in a clinical setting with their patients. Additionally, this research may impact the collaboration between cardiology and genetic providers, especially in a pediatric setting. This research was conducted during the development of the Cardiovascular Genetics Clinic at UPMC Children's Hospital of Pittsburgh, which is multidisciplinary approach to patient care; similar models have been adopted by pediatric institutions throughout the United States. This type of clinic often involves a genetic counselor who performs important tasks including taking a detailed family history, educating families about the option genetic testing, having a comprehensive discussion regarding its risks and benefits, and offering information regarding insurance coverage or alternative financial options for genetic testing. While these factors are instrumental to the genetic counseling pre-test process, a traditional cardiology clinic may not have the proper time or resources for a thorough discussion. The ultimate goal of the study is to explore possible gaps in patient care and education in regards to genetic testing, which has the potential to be addressed by a multidisciplinary model like the Cardiovascular Genetics Clinic,

in order to reduce barriers that may prevent pediatric patients and their families from pursuing genetic testing for HCM.

3.2 METHODS

3.2.1 Participants

The target population for this survey included parents or guardians of HCM patients who have been seen by the Division of Cardiology at UPMC Children's Hospital of Pittsburgh. The Division of Cardiology has been maintaining a Microsoft Excel spreadsheet of its patients since January 2017; participants were recruited using this data. Prior to gaining access to this patient information, the study was reviewed and approved by the University of Pittsburgh Institutional Review Board (IRB) committee (Appendix A). Researchers were granted access to this spreadsheet upon IRB approval. For each patient, information that was found within this document included name, date of birth, medical record number, diagnosis information, sex, and race/ethnicity. A medical record review was performed utilizing this information to verify diagnoses and record contact information for each patient and their family. Physical mailing addresses, phone numbers, and email addresses (for families who disclosed their email addresses in their medical record) were recorded during the medical record review. The genetic testing status of each patient was also recorded.

There were 113 patients identified with a diagnosis of HCM. The following criteria for the exclusion of patients included: a diagnosis of HCM secondary to another condition (e.g., genetic diagnosis like Fabry, mitochondrial disease, etc.), the family had moved, the patient had been

discharged from care by the Department of Cardiology at Children's Hospital, positive genetic diagnosis but failure to meet clinical diagnostic criteria for HCM, or other complex social situations. For example, one individual was omitted from the study when medical record review indicated that this individual had lost both parents to heart conditions. Another individual omitted from the study had severe intellectual disability and now was living in an adult group home. Age was an important consideration regarding the study population, as the focus of the study was genetic testing in pediatric HCM patients. However, if the patient had been seen recently and it appeared that the patient lived with their parents, then a recruitment letter was sent to their household, even if the patient was 18 years or older at the time of study initiation.

After exclusion criteria was applied to this population, 70 patients which comprised 63 households were eligible for the study. Since some individuals were siblings of one another, participants were instructed to fill out the survey in reference to their most recently diagnosed child.

3.2.2 Survey Development

The survey that was created for this study was adapted from Khouzam et al. (2015) (Appendix B) with permission. It was reviewed and edited by two genetic counselors, a cardiologist, and a statistician during its development. The survey was published as an online questionnaire utilizing Qualtrics software, which was accessed through a University of Pittsburgh license.

The survey is comprised of five sections: introduction and consent, general diagnosis and family history, genetic evaluation, attitudes towards genetic testing, and demographic information. The introduction and consent section contained information about the survey, potential risks and

benefits, and contact information of the primary researcher. To continue with the survey, participants had to consent to the survey in this section. The next section of the survey was general diagnosis and family history, in which the participant provided information regarding their child's age and diagnosis, family history of HCM and/or sudden cardiac death, and personal perception of risk and surveillance history. The genetic evaluation section of the survey queried about whether or not the participant's child had genetic testing. For participants who said yes, they were asked follow-up questions regarding who their child's healthcare providers were, the result of the genetic test, and the ways that genetic testing was valuable or not for their child. For participants whose child did not have genetic testing, follow-up questions included whether or not they were interested in testing, the reasons that they have not pursued genetic testing, and what information they would like to know before pursuing genetic testing for their child. The next section of the survey, attitudes towards genetic testing, elicited participants' perceptions regarding main risks and benefits of genetic testing. Additionally, participants were asked to respond to statements formatted in a 5-point Likert-style scale (strongly agree, somewhat agree, neither agree nor disagree, somewhat disagree, and strongly disagree) about various attitudes, beliefs, and facts regarding genetic testing. The final section asked participants about demographic information regarding their child and their family. Questions elicited information about the child's age, race, and sex; additional questions inquired about classification of the family's home community, distance from UPMC Children's Hospital of Pittsburgh, and insurance coverage information.

Skip logic was utilized throughout the survey, so participants would only be shown questions that were relevant to answers they previously provided. The survey was made available via an anonymous web link.

3.2.3 Survey Recruitment and Distribution

The survey was initially distributed via a recruitment letter mailed in October 2018 (Appendix C). The letter was signed by Dr. Mousumi Moulik, who is a member of the cardiology clinical team. This letter briefly explained the project and its purpose and included an anonymous link for the survey, as well as the primary researcher's contact information. Of the 63 households to which the survey was distributed, 40 families had email addresses listed in the electronic medical record system. Following the distribution of the recruitment letters, reminder emails were sent to these 40 households; the first reminders were sent in November 2018 and second reminder emails were sent in December 2018 (Appendix D). The survey remained open for four months, from October 2018 to February 2019.

3.2.4 Data Analysis

Descriptive statistics, including means, ranges, and response frequencies, were performed on the anonymous survey responses utilizing Microsoft Excel software. Data were analyzed and presented in the context of comparison between participants who pursued genetic testing for their children and participants who did not pursue genetic testing for their children, who will be designated as +Genetic Testing and -Genetic Testing, respectively, for sake of ease for the remainder of this document. Incomplete survey responses were included in survey analysis when participants answered the specific question and there was no reason to question the information that they provided.

3.3 RESULTS

3.3.1 Demographic Information

The survey was distributed to 63 households that had one or more children affected with HCM and 13 provided partial or full responses, yielding a 21% response rate. Of the 13 responses, 11 respondents finished the survey to completion. Respondents, who were the parents or guardians of the child, were asked the age, sex, race/ethnicity, and health insurance of their affected child. The mean age of affected children in this population was 10.1 years with a range of 3 years to 20 years. The majority of respondents, 81.8%, had male children affected with HCM. All respondents indicated that their child had health insurance; 60% had private insurance, while 40% had medical assistance. One individual did not indicate whether or not their child had insurance nor what type (Table 1).

Additional information was collected about the characteristics of families who responded to the survey. The majority of survey respondents' families live in a rural community (54.5%). Also, the majority of survey respondents indicated that one parent works in the healthcare or medical field (63.6%). Of note, no respondents indicated that their child affected with HCM was adopted and/or in foster care (Table 7, Appendix E).

Table 1 Demographic Information

Variable	+Genetic Testing	-Genetic Testing	Total
Age (years)			
Mean±SD	8.8±5.9	11.3±7.0	10.1±6.3
Range	4.0-20.0	3.0-16.0	3.0-20.0
Sex			
Female	16.7% (1)	20.0% (1)	18.2% (2)
Male	83.3% (5)	80.0% (4)	81.8% (9)
Race/Ethnicity			
Caucasian	83.3% (5)	40.0% (2)	63.6% (7)
African American	0% (0)	40.0% (2)	18.2% (2)
Other	16.7% (1)*	20.0% (1)**	18.2% (2)
Health Insurance			
Private Insurance	60.0% (3)	60.0% (3)	60.0% (6)
Medical Assistance	40.0% (2)	40.0% (2)	40.0% (4)

* Hispanic, **Mix

3.3.2 Genetic Evaluation

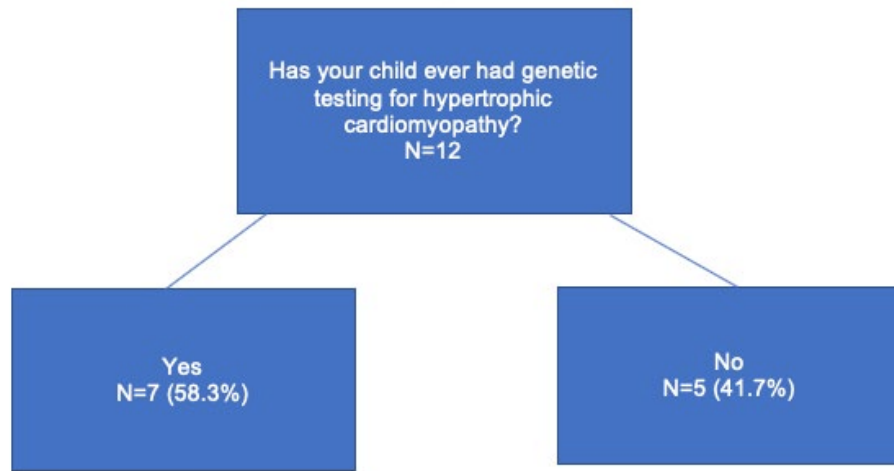


Figure 1 Genetic Testing Status

Respondents were asked questions about whether or not their child had received genetic testing and 58% of respondents said their child had received genetic testing for HCM, while 42% said their child had not (Figure 1). The parents who indicated that their child had received genetic testing were asked questions distinct from those who indicated that their child had not received genetic testing. However, both groups were asked about the healthcare professional(s) who follow their child for the HCM diagnosis, which is summarized in Table 2.

Table 2 Healthcare Providers for HCM

	+Genetic Testing	-Genetic Testing	Total
Who does your child see for hypertrophic cardiomyopathy?			
Cardiologist	100% (6)	100% (4)	100% (10)
Geneticist	33.3% (2)	0% (0)	20.0% (2)
Genetic Counselor	16.7% (1)	25% (1)	20.0% (2)
Primary Care Physician	0% (0)	25% (1)	10% (1)

3.3.2.1 +Genetic Testing

Families who indicated that their child had received genetic testing were asked if they had requested genetic testing or whether their healthcare provider recommended it. 100% of respondents said that their healthcare provider recommended the genetic test. Of the seven participants whose child had genetic testing, one indicated their child had a positive result, one indicated a negative result, one indicated a variant of uncertain significance, and four indicated that they are not sure of the result. It is not possible to discern from the survey results whether these four individuals were not able to understand their child's genetic test result, or if their child's testing results were not yet available. However, one of these four participants indicated in the survey that their child's testing was still in progress, which is why that participant indicated "not sure" as a response.

Participants who pursued genetic testing for their child were also asked open-ended questions about their experience with genetic testing, specifically regarding what ways genetic testing was valuable and not valuable (Table 3).

Table 3 Value of Genetic Testing

In what ways, if any, was your child's genetic testing...?	Valuable	Not Valuable
Parent 1	It ruled out several other known causes of related health issues	It did not provide an answer to the cause of her issues
Parent 2	To prove he had the same mutation as his grandmother	None
Parent 3	Understanding the risk of passing the mutated genes to offspring	Not knowing if the mutated genes was the cause of HCM
Parent 4	We found that he's a carrier of CF that is all. Otherwise, it was not helpful.	We never did find the mutation, so we still have no cause.
Parent 5	To know for sure he had the heart condition	*

*Parent 5 did not respond to this item.

3.3.2.2 -Genetic Testing

Whenever participants indicated that they had not pursued genetic testing for their child, they were next asked if they were interested in genetic testing. Additionally, they were asked to specify the main reasons for not pursuing genetic testing at this time (Figures 2 and 3). Based on the responses from both questions, 4 participants out of 5 participants who had not pursued genetic testing expressed interest in doing so (80%, standard error = 0.179). (Of note, one respondent indicated both interest and no interest in pursuing genetic testing.)

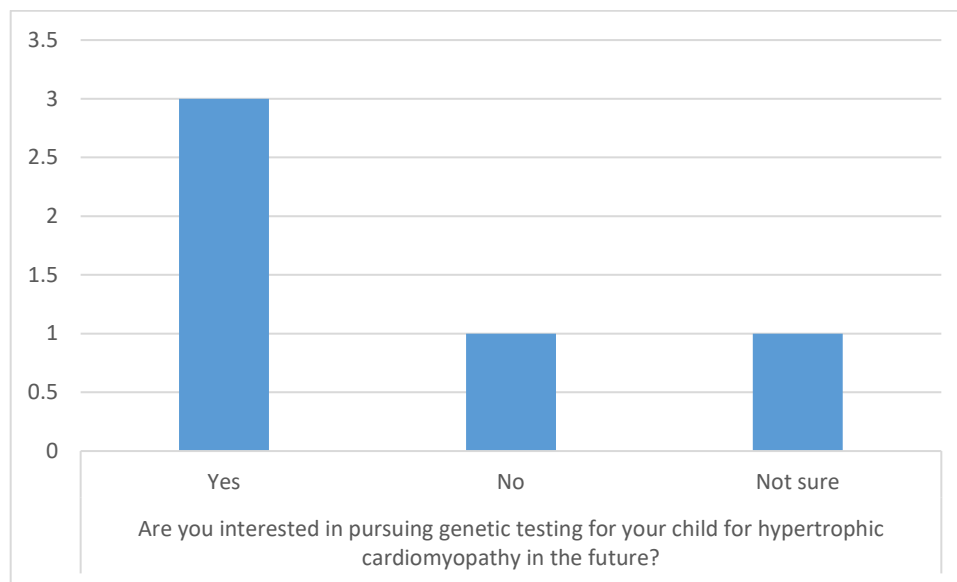


Figure 2 Interest in Genetic Testing

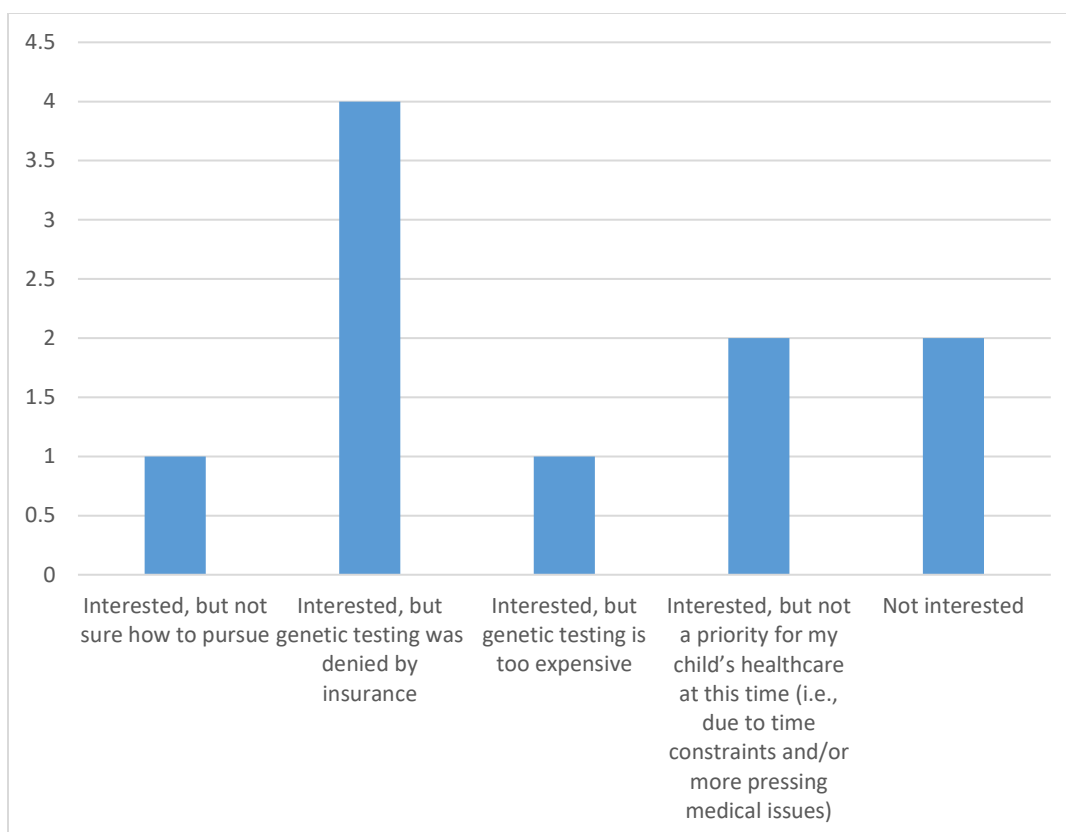


Figure 3 Reasons for Not Pursuing Testing

Lastly, participants were asked if there was anything they would like to know about genetic testing before making their decision about pursuing it for their child. One participant responded, and asked, “Will they test my other children?”

3.3.3 Diagnosis and Family History

Another section of the survey contained questions regarding the events surrounding the child’s diagnosis of HCM, including at what age and how they were diagnosed (Table 4). For the participants who indicated “other,” the reasons cited included “diagnosed at birth with difficulty breathing” and “discovered by chance during a visit to ER for upper respiratory infection (via chest x-ray)”. The majority of +Genetic Testing as well as total children diagnosed with HCM were

diagnosed most frequently through the detection of a murmur or heart problem upon routine check-up (71.4% and 58.3%, respectively). However, for the -Genetic Testing group, the majority had a family history of HCM, which prompted a cardiac evaluation (60%).

Table 4 Diagnosis Information

Variable	+Genetic Testing	-Genetic Testing	Total
How old was your child when he/she was diagnosed?			
Mean±SD (years)	8.0±6.7	2.2±3.9	5.4±6.1
Range (years)	Birth – 15	Birth – 8	Birth – 15
Why was your child originally referred to be evaluated for hypertrophic cardiomyopathy?*			
A murmur or heart problem was detected upon routine checkup	71.4 % (5)	40.0% (2)	58.3% (7)
Family history – cardiac (heart) evaluation was done	0.0% (0)	60.0% (3)	25.0% (3)
Child was having symptoms (dizziness, chest pain, fainting, palpitations, shortness of breath, other)	14.3% (1)	20.0% (1)	16.7% (2)
Other	28.6% (2)	0.0% (0)	16.7% (2)

*Participants could select multiple responses and therefore, the total does not add up to 100%.

Table 5 Sibship of Affected Child

	+Genetic Testing	-Genetic Testing	Total
Do you have other children?			
Yes	85.7% (6)	40.0% (2)	66.7% (8)
Affected	0.0% (0)	100.0% (2)	25.0% (2)
Unaffected	100.0% (6)	0.0% (0)	75.0% (6)
No, but I am planning on having more children	14.3% (1)	20.0% (1)	16.7% (2)
No, and I am not planning on having more children	0.0% (0)	40.0% (2)	16.7% (2)

Participants were also asked if they had any other children besides their child affected with HCM (Table 5). Most of the +Genetic Testing participants have other children (85.7%), while the majority of -Genetic Testing participants do not (60%). As shown in Table 5, for the respondents who do have children, 25% of the total individuals have a second child who is affected.

Additional questions were asked of participants regarding family history. Participants who did indicate a family history specified affected family members, which included grandparents, aunts/uncles, and cousins (Figure 4). Participants who indicated their child had a family history of HCM were also asked how many people, other than their affected child, were diagnosed with HCM. One participant in the +Genetic Testing group said that one other family member was affected, while another participant said two other family members are affected. The three participants in the -Genetic Testing group with a family history responded that they had two, five, and seven or eight other family members diagnosed with HCM.

Figure 5 indicates the frequency of responses regarding whether or not individuals think that they are at risk for HCM based on their child's diagnosis. Another way perceived risk was assessed was by asking whether or not participants have been screened for HCM (Table 6). Most participants in both groups indicated that they have been screened in some way at this time (66.7%). Of note, 100% of participants said that they had been counseled regarding the way that HCM can be passed down through a family.

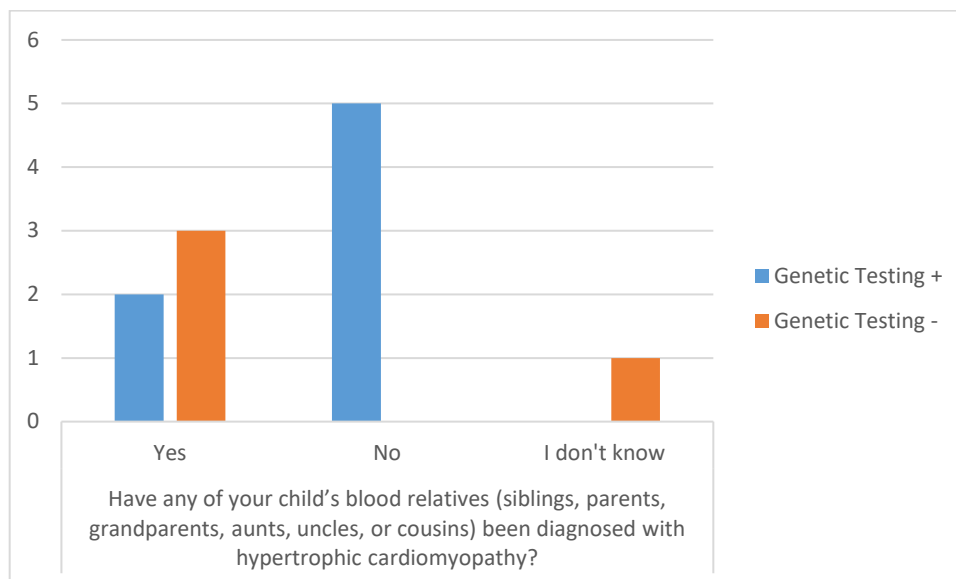


Figure 4 Family History of HCM

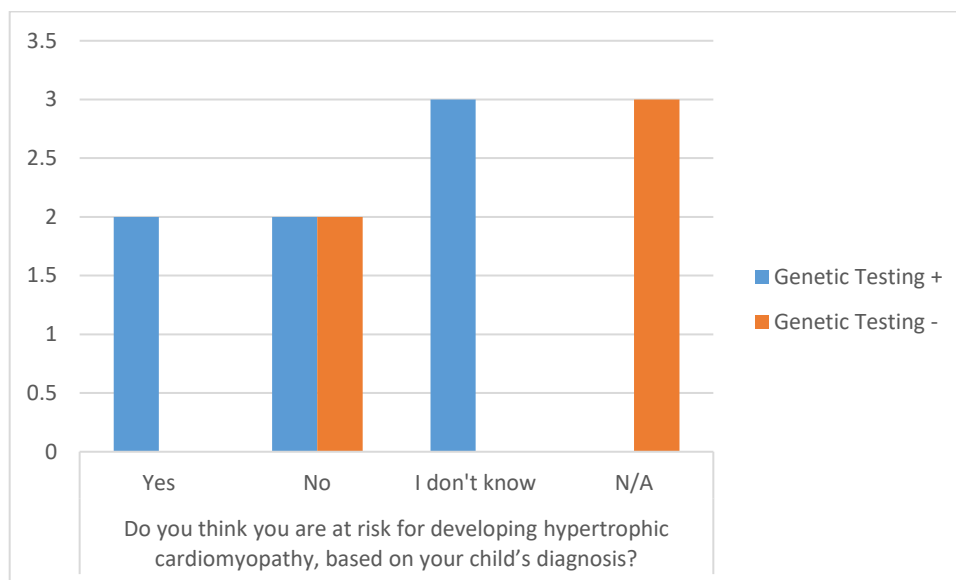


Figure 5 Perceived Risk of HCM

Table 6 Cardiac Screening

	+Genetic Testing	-Genetic Testing	Total
Have you been screened for hypertrophic cardiomyopathy?			
Yes, I saw a cardiologist	71.4% (5)	60.0% (3)	66.7% (8)
Yes, I had an echocardiogram	71.4% (5)	40.0% (2)	58.3% (7)
Yes, I had an electrocardiogram	57.1% (4)	40.0% (2)	50.0% (6)
Yes, I had a Holter monitor	42.9% (3)	40.0% (2)	41.7% (5)
Yes, I had genetic testing	28.6% (2)	0.0% (0)	16.7% (2)
No, I have not been screened at this time	28.6% (2)	40.0% (2)	33.3% (4)

3.3.4 Risks and Benefits

Respondents (N=11) were asked about the main risks and benefits of genetic testing. Benefits cited by respondents included identifying family members at risk to develop HCM (N=9, 81.8%); relief, from gaining knowledge and potentially having a definitive answer (N=9, 81.8%); contributing to genetic information and/or research (N=8, 72.7%); providing a more complete understanding of their child's HCM diagnosis (N=8, 72.7%); and helping to direct care for their child for HCM (N=5, 45.5%).

Risks of genetic testing that respondents cited were financial cost (N=8, 72.7%); possible future discrimination by employers and/or insurance (N=3, 27.3%); time-consuming, lengthy process, (N=3, 27.3%); incidental findings (N=3, 27.3%); and anxiety and distress, from waiting for the result and/or its implications for their child and family (N=3, 27.3%).

3.3.5 Attitudes and Beliefs

All respondents were asked to complete a Likert-scale portion of the survey, which aimed to elicit family attitudes towards, experience with, and knowledge regarding genetic testing. The wording was dependent on whether or not the participant's child had genetic testing (Table 8, Appendix E) or did not have genetic testing (Table 9, Appendix E). The statements posed to participants were similar in construction in order to facilitate comparison between the two groups.

The purpose of the statements posed in this section of the survey was to gather additional information regarding factors that either motivated or deterred families from pursuing genetic testing. For example, both groups were asked whether or not they pursued (+Genetic Testing) or would pursue (-Genetic Testing) genetic testing to learn more about the risk of HCM for their other children (e.g., their affected child's siblings) (Figure 6). Additional factors that were elicited to determine whether or not they had/would have had an impact on genetic testing included advisement by healthcare professionals, requests from family members, motivation to gain information on personal (parental) HCM risk, motivation to gain information on HCM risk for other family members, health insurance coverage, accessibility, and possible negative impact.

Lastly, this section contained one item that assessed awareness and understanding by stating the general basis of Genetic Information Non-Discrimination Act, or GINA, and the protections it provides for patients who undergo genetic predisposition testing (Figure 7). This item was not only elicited to determine if awareness appears to impact the decision whether or not individuals pursued genetic testing, but also assessed if participants were informed of this law.

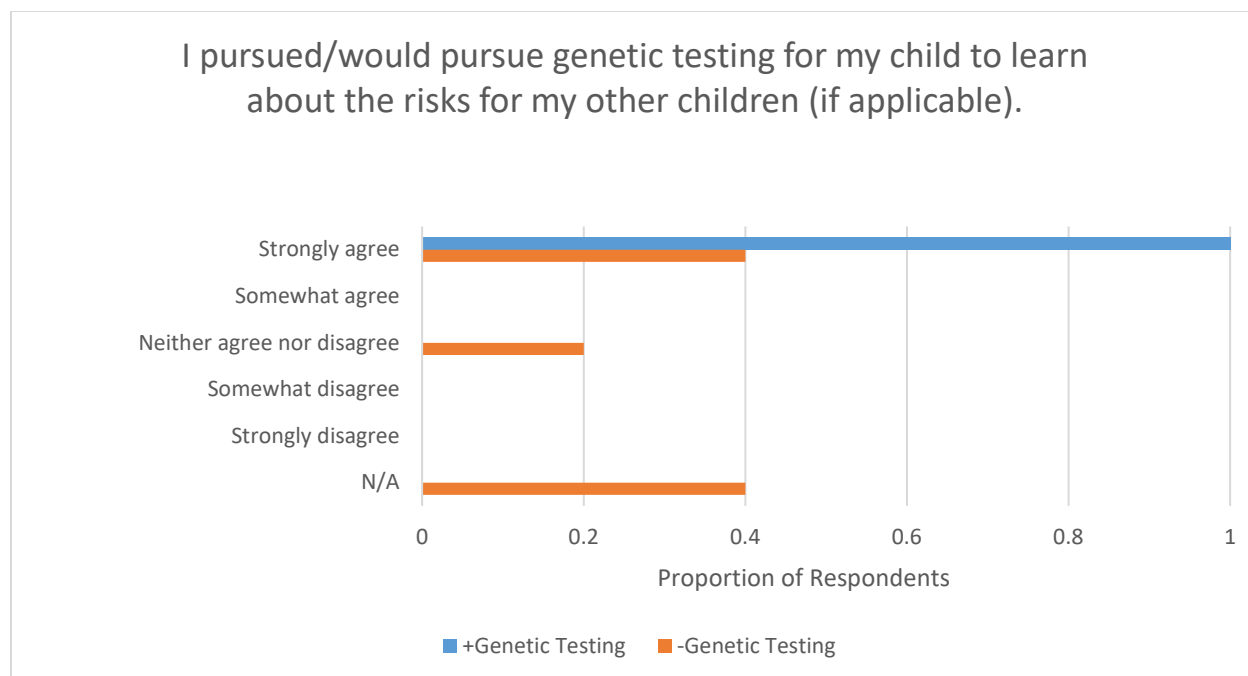


Figure 6 Impact of Siblings' Risks on Affected Child's Genetic Testing Status

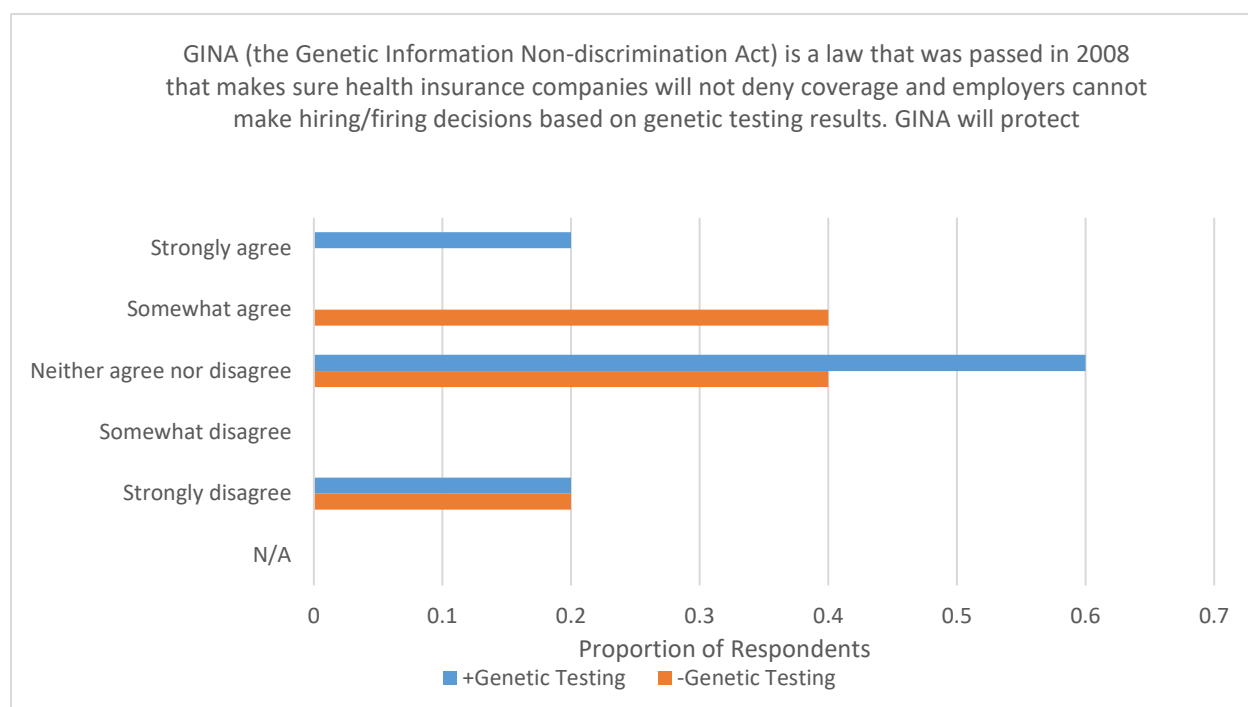


Figure 7 Perception of GINA

The statements in the final section of the survey aimed to elicit perceptions on the information that can be gained from genetic testing (Tables 10 and 11, Appendix E). Similar to the previous section, the participants had different wording based on whether or not their child had genetic testing, but the items for both groups were worded in a similar manner. The primary difference between the way that items were framed between the +Genetic Testing and -Genetic Testing groups is the fact that +Genetic Testing participants were posed statements based on the actual impact that genetic testing had on their family, while the statements for the -Genetic Testing group were framed in a manner in which they were asked to cite their perceptions regarding genetic testing.

Within this section, some statements focused on psychosocial factors, including whether genetic testing caused/would cause anxiety and distress (Figure 8), relief, and/or concern regarding health insurance coverage. Additionally, other items in this section were targeted to gain more information regarding the impact of genetic testing on behavior changes, including whether or not genetic testing encouraged/would encourage the family to take action towards a healthier lifestyle and whether or not genetic testing helped/would help the family make better healthcare decisions.

The final statement in this section to which participants responded elicited attitudes regarding the helpfulness of genetic testing (Figure 9), in the context that all of the affected children already had clinical diagnoses of HCM. This item elicited the comparison between groups to determine whether or not the +Genetic Testing group found genetic testing helpful, and if the -Genetic Testing group perceived genetic test results to be informative. Like the aforementioned GINA item in the previous section, this statement also elicits an education piece (e.g., whether or not participants were educated on and/or are aware of the benefits of genetic testing in the information it can offer a patient and their family).

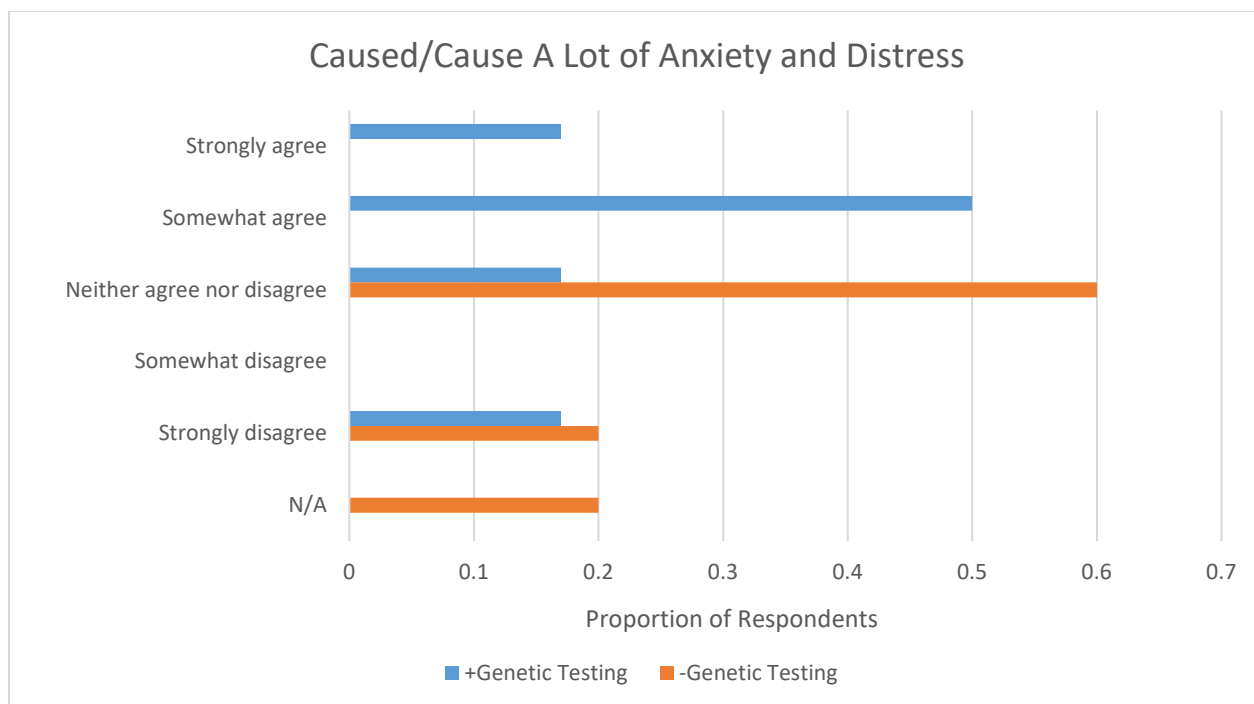


Figure 8 Impact of Anxiety & Distress on Genetic Testing Status

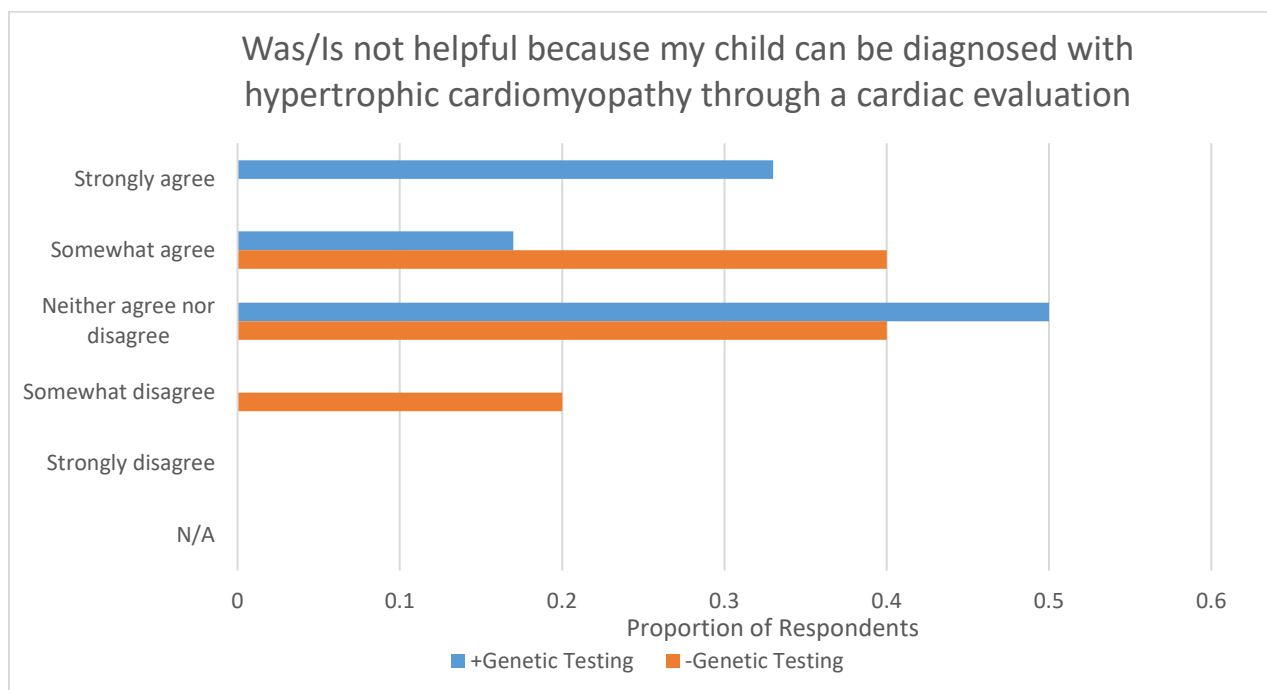


Figure 9 Perception of the Usefulness of Genetic Testing

3.4 DISCUSSION

3.4.1 Demographic Information

Although the number of respondents was small and statistical analysis could not be conducted, the -Genetic Testing group was associated with more racial and ethnic minorities than the +Genetic Testing group. Previous studies have identified barriers to genetic testing that are associated with racial and ethnic disparities (Suther and Kiros, 2009; Forman and Hall, 2009). One study determined that differences in knowledge regarding genetic testing, levels of mistrust, and health insurance coverage can exist in different races and ethnic groups (Suther and Kiros, 2009). Both groups who pursued and did not pursue genetic testing had equal frequencies of individuals who had private insurance and Medicaid. Therefore, this reduces insurance as a potential barrier, although individuals did cite insurance denial and cost as reasons why they did not pursue genetic testing in this study. Insurance companies have different requirements regarding genetic test coverage. For example, many insurance companies mandate pre-test genetic counseling. If this does not occur, then there is the possibility that the genetic test will get denied (Stenehjem et al., 2018).

3.4.2 Genetic Evaluation

A study by Khouzam et al. (2015) found that seeing a genetic professional was considered a predictor of whether or not HCM patients have had genetic testing. However, in the current study, individuals from both groups had seen genetic professionals.

3.4.2.1 +Genetic Testing

Similar to previous research, the current study found that a family's healthcare provider could be a motivator for genetic testing (Anderson et al., 2012; Delikurt et al., 2014). Every individual in the +Genetic Testing group said that their healthcare provider recommended genetic testing.

Statements made by respondents in this section of the survey illustrated important concerns regarding certain risks and misconceptions about genetic testing. For example, one respondent designated as Parent 5, said that genetic testing was valuable because it confirmed he had a heart condition. However, it is important to emphasize to families even in the event of negative genetic testing, a child who is clinically diagnosed with HCM still has that diagnosis regardless of the genetic test result. Multiple parents indicated that genetic testing was not valuable because it did not identify an answer for their child, since it did not identify a pathogenic variant associated with HCM. Lastly, four out of six parents indicated that they are not sure of their child's genetic test result. As previously mentioned, it was unclear whether this response was due to the fact that the results have not yet been disclosed or a lack of understanding of what their child's genetic test result means. These statements and data indicate that even families who have pursued genetic testing may have a misunderstanding regarding the information genetic testing can provide and its result.

3.4.2.2 -Genetic Testing

One of the primary aims of this study was to elicit barriers to genetic testing in this patient population. Interestingly, four out of five respondents who did not pursue genetic testing for their child indicated some type of interest in genetic testing; this may suggest that barriers to testing do exist for this population. The most commonly cited reason for not pursuing testing was that genetic

testing was denied by insurance, which is consistent with prior research (Vande Wydeven et al., 2012; Anderson et al., 2012). Other reasons included cost, uncertainty of how to attain testing, and more pressing health concerns for their child. These concerns have been identified in previous research in multiple genetic counseling practice settings and across diverse populations (Vogel et al., 2018; Kutscher et al., 2017; Beene-Harris et al., 2007). The majority of these barriers are considered institutional barriers to access rather than individual barriers.

3.4.3 Diagnosis and Family History

One finding regarding the family history was that participants who had not pursued genetic testing reported a greater frequency of family history when compared to participants who pursued genetic testing. In previous studies, family history of conditions has been a predictor for individuals pursuing genetic testing; this has been established across different types of genetic counseling practice settings (Wessel et al., 2016; Khouzam et al., 2015). However, one study did cite that a barrier to genetic testing was the failure on the healthcare professional's part in obtaining a detailed family history (Delikurt et al., 2014). This finding requires further investigation. For example, it would be useful to know whether these individuals had been offered genetic testing and whether their health care providers were aware of the HCM family history. These issues were not explored in this research study. Additionally, two individuals who had not pursued genetic testing for their child also said they had other children who were affected with HCM, while participants who had pursued genetic testing for their children did not have any other children who were affected. This provides further evidence that family history was possibly not related with pursuing genetic testing in this study.

3.4.4 Risks and Benefits

The risks and benefits of genetic testing were elicited from all respondents. The data collected were consistent with other perceived risks and benefits that have been elucidated in other studies. For example, the most frequently cited perceived benefit of genetic testing was identifying family members at risk to develop HCM. The second most frequently cited perceived benefit was providing a more complete understanding of a child's HCM diagnosis, which is congruent with a previous qualitative study that found individuals were enthusiastic about genetic testing because it can potentially reduce diagnostic uncertainties (McGowan et al., 2013).

In terms of risks that were found by this study, financial cost was the most frequently noted perceived risk. As previously mentioned, insurance coverage and cost were identified as major reasons that the -Genetic Testing respondents did not pursue genetic testing; this risk remained consistent across both individuals who did and did not pursue genetic testing. An additional perceived risk included possible future discrimination by employers and/or insurance, which was cited by three individuals. This indicates that these individuals may be unaware of or misunderstand the Genetic Information Non-Discrimination Act, or GINA, which protects individuals who pursue genetic testing from discrimination from employers and health insurance based on their result. This remained consistent throughout the survey and will be discussed further in the next section.

3.4.5 Attitudes and Beliefs

An apparent motivator for pursuing genetic testing for this specific population is to learn about risk for other children. All respondents who had pursued genetic testing for their child

strongly agreed that they pursued it to learn about the risks for their other children. However, only 40% in the group that did not pursue genetic testing said that it was a motivator for them. Responses regarding other factors that could potentially be motivating or deterring to pursuing genetic testing that were assessed were overall comparable between both groups.

A number of respondents cited that genetic testing resulted in anxiety and distress. Four respondents (66.7%) either strongly or somewhat agreed with the statement that the information gained from their child having a genetic test for HCM caused a lot of anxiety and distress. Furthermore, three respondents (50%) strongly agreed with the statement that the information gained from their child having a genetic test for HCM made them concerned about their child's, their own, and/or other family members' future health insurance coverage. For participants who did not pursue genetic testing, none agreed with the statement that genetic testing would cause anxiety and distress. Thus, anxiety and distress seem like unlikely barriers for those who did not pursue genetic testing; it appears that genetic testing may have caused anxiety for families who pursued it. However, information regarding the participants' anxiety levels before testing was not assessed.

Another interesting finding within the attitudes and beliefs section of the study was all respondents who had attained genetic testing for their child either agreed or were neutral regarding the statement that their child's genetic testing was not helpful because their child was already diagnosed with HCM. For individuals who did not pursue genetic testing, 80% of participants agreed with this statement. This trend is consistent with prior cardiogenetic research which has found that families encounter difficulty understanding the results of genetic testing. Furthermore, a study conducted by Ormondroyd et al. (2013) indicates that families who do not have an

understanding of the results of genetic testing are less likely to share the genetic test result with at-risk family members than families who do understand the result.

In regard to discrimination, it is possible that respondents are not aware or do not understand GINA. Only 20% of individuals who had pursued genetic testing for their child and 40% who had not pursued genetic testing for their child agreed with the statement, “GINA (the Genetic Information Non-discrimination Act) is a law that was passed in 2008 that makes sure health insurance companies will not deny coverage and employers cannot make hiring/firing decisions based on genetic testing results. GINA will protect my child from future discrimination and unlawful termination of employment and ensure their access to health insurance.” There are a couple of potential explanations for these results. One possibility is a lack of awareness or misunderstanding of GINA, which would be consistent with a prior study that showed the majority of patients in their population were not aware of this law (Cragun et al., 2019). Another possible explanation is that respondents are aware and educated on GINA but interpreted the statement from the perspective of the permanence of GINA (e.g., GINA may not exist in the future to protect my child from discrimination). Like the anxiety and distress measure, it does not appear that a lack of familiarity with GINA and/or uncertainty of its permanence was a barrier to genetic testing in this population. However, it does appear that GINA and its relationship to discrimination should be addressed in both pre- and post-counseling sessions, to aid in decision-making as well as to help parents understand the impact of genetic testing results on their child’s future.

3.4.6 Study Limitations

There are several limitations to this study. The main limitation of this study was the small sample size of respondents to the survey. Inferential statistics were not appropriate given the small

sample size. Thus, it could not be determined whether or not there were any statistically significant trends within this sample, or statistical differences between the +Genetic Testing and -Genetic Testing groups for any of the variables that were assessed.

Another limitation of this study is that its results are most likely not generalizable to other populations, specifically for other pediatric heart conditions. When determining the scope of this study, there was an opportunity to survey a larger patient population of pediatric patients with cardiac conditions. However, many inherited conditions are approached differently by healthcare providers. Thus, different barriers may exist for specific heart conditions. For example, cardiac conditions like Long QT syndrome, which are more frequently genetic, are intuitively more likely to be offered genetic testing. The inclusion of multiple inherited cardiac conditions would have possibly allowed for a larger population and more informative comparisons, but the data may have been different depending on the condition and thus inappropriate to combine. The scope of the study was focused on HCM specifically since it is considered the most common inherited cardiac condition, thus allowing for the largest possible sample while looking at one condition.

A third limitation of this survey is the fact that timing of the genetic testing discussion by a healthcare provider with patients' families was not explicitly elicited. If a healthcare provider brings up genetic testing at the first visit, which is typically the same time as the initial diagnosis of HCM for the patient, this potentially may have been the reason that it was not pursued (e.g., family had too much to think about). Furthermore, perhaps it was not considered because the cardiologist brought it up at that first visit with minimal information and/or informed consent because there was too much to review. Conversely, if there is a follow-up visit with more time and space to discuss genetic testing, parents may be more inclined to pursue at that time. This piece of information is a potential barrier to genetic testing and would be useful to incorporate to help

further determine why some families do or do not pursue genetic testing. Future studies focused on this topic should include analysis of this timing factor, and it may even be beneficial to survey healthcare providers to determine when they typically have this conversation and why.

Lastly, this study is also limited by its use of an anonymous survey. Thus, the data cannot be linked to individuals' medical record review. For this reason, researchers relied on self-reported data, and the information provided by participants was unable to be confirmed by a medical record review.

3.4.7 Future Directions

This research study offers preliminary evidence to indicate that individuals with children with HCM may not have complete understanding and awareness regarding genetic testing options for their child. A reasonable direction for future research would include studying the impact of the implementation of a cardiovascular genetic clinic on patient access, awareness, and understanding of genetic testing, as compared to this patient population. Additionally, given the research findings that both parents who did and did not pursue genetic testing do not have a complete understanding of GINA, it is possible that this law is not routinely explained to families. There is limited research on this topic in regard to patient and physician awareness; only a handful of studies were found that explored this topic (Allain et al., 2012; Cragun et al., 2019; Dorsey et al., 2013; Laedtke et al., 2012; Parkman et al., 2015). It is important that the understanding of both healthcare providers who offer genetic testing as well as families who are pursuing genetic testing be further explored. Thus, a survey of cardiovascular healthcare providers, including cardiologists, genetic counselors, nurse practitioners, etc., would be useful to determine what information they communicate to their patients regarding genetic testing.

Another direction for future research presented by this study is to look at insurance more closely in its role as a potential barrier to genetic testing for pediatric patients with HCM. Insurance denial was the primary reason that families did not pursue genetic testing. However, participants who pursued and did not pursue genetic testing had equal frequencies of individuals who had private insurance and Medicaid. Additionally, several prior studies across genetic counseling practice settings have also elucidated insurance as a barrier to testing (Vande Wydeven et al., 2012; Kutscher et al., 2017; Spoonamore and Johnson, 2016). Given these findings, it may be useful to specifically analyze the types of private insurance and their policies on genetic testing, as well as compare the similarities and differences between families who had genetic testing approved and families who had genetic testing denied. This will gather more information on the specific reasons that insurance companies deny coverage of testing, so institutions can address these to reduce the chance of insurance denial of testing.

As genetic testing becomes more widespread and attitudes about testing change, it is anticipated that the number of individuals who are offered genetic testing will increase. Additionally, more genetic counselors may practice in cardiovascular settings, and insurance companies may more readily cover testing as it becomes a standard of practice. Thus, it may be inappropriate for future studies to build on this research; rather, it may be more beneficial to use it as a comparison if the barriers that this study elucidated are no longer issues, and other barriers arise.

3.5 CONCLUSION

This study offers preliminary data regarding possible barriers to genetic testing in families of pediatric hypertrophic cardiomyopathy patients. It provides directions for future research to explore in larger patient populations and additionally helps clarify perceived risks and benefits of families who have pursued genetic testing for HCM.

The first aim of the study was to survey the parents and/or guardians of pediatric patients with HCM that have been seen by pediatric cardiology at UPMC Children's Hospital of Pittsburgh and received a clinical diagnosis of HCM. The survey had a 21% response rate, and the sample was about equally represented by parents who had pursued and who had not pursued genetic testing for their child.

The second specific aim of this project was to analyze the survey data to elicit the reasons parents and/or guardians do not pursue genetic testing for their children. Based on the responses that questioned the interest in genetic testing of respondents who had not pursued genetic testing for their child, it was determined that 80% were interested in moving forward with testing. The primary reasons testing was not pursued as well as perceived risks of genetic testing included insurance denial of testing, financial concerns, and cost of testing. Additional reasons identified included uncertainty regarding how to pursue genetic testing and other priorities with respect to their child's health and family. Apparent facilitators to genetic testing in this study included concern regarding HCM risk for other children and healthcare providers recommending genetic testing, both which 100% of participants who had pursued genetic testing cited.

The final aim of this project was to identify barriers so that strategies to reduce these barriers can be incorporated into the newly formed Cardiovascular Genetics Clinic at UPMC Children's Hospital of Pittsburgh. For example, the provision of genetic counseling services for

each cardiology patient would possibly reduce several of the identified barriers. Genetic counseling can provide the time and resources to obtain a detailed family history, thoroughly educate a family on the risks and benefits to genetic testing, increase the likelihood to obtain insurance coverage, and explore alternative finance options. Additionally, this research can allow clinicians to better target certain areas of discussion regarding genetic testing. One finding of this study is that participants who had and had not pursued genetic testing for their child lacked awareness and knowledge regarding GINA. Based on this data, an impactful adaptation to the typical genetic testing pre-test and post-test counseling would include an in-depth discussion and resources to explain GINA.

While the generalizability of these results to other populations is limited, this research provides preliminary data for the necessity of clinicians to educate and provide genetic testing options for their patients. Additional studies may be warranted in order to further investigate the differences between groups of families who have and have not pursued genetic testing, to determine whether or not they approach statistical significance for any of the variables that have been assessed in this study. As genetic testing and genetic counseling continues to evolve and become more widespread, it is possible that these barriers will decrease, and knowledge, awareness, and coverage of genetic testing will improve.

4.0 PUBLIC HEALTH AND GENETIC COUNSELING SIGNIFICANCE

4.1 RESEARCH SIGNIFICANCE TO PUBLIC HEALTH

Understanding the barriers to genetic services for pediatric HCM patients and their families is the first step to implementing a plan to alleviate these barriers and improve access for patients at UPMC Children's Hospital of Pittsburgh. One of the core functions of public health is assurance, which is defined as, "promoting and protecting public interests through programs, events, campaigns, regulations and other strategies, and making sure that necessary services are provided to reach agreed upon goals" (Institute of Medicine, 1988). The purpose of this study was to identify perceptions of genetic testing and possible barriers to genetic testing for families of pediatric HCM patients at UPMC Children's Hospital of Pittsburgh. Thus, identifying these barriers promotes assurance that genetic counseling and genetic testing are being offered consistently to pediatric HCM patients. Based on the collected data, pediatric patients typically meet with a cardiologist only, who is responsible for discussing and coordinating genetic testing. A genetic counselor is not usually available to meet with every HCM patient. Based on this study, some families did have genetic counseling and genetic testing while other families did not. While it is uncertain based on this data whether or not all families were offered genetic services, one concern is that some families are not provided genetic services. In order to mitigate this concern, a reasonable outcome would be to promote more consistency among all cardiology healthcare providers to ensure that their patients are offered genetic testing and provided insurance authorization by their provider, as well as adequate education to ensure sufficient/appropriate understanding of the risks, benefits, and information that genetic testing provides.

One of the essential services within the core function of assurance is to, “evaluate effectiveness, accessibility, and quality of personal and population-based health services” (Institute of Medicine, 1988). This study evaluated the barriers to genetic services and found that 80% of participants who did not pursue genetic testing for their child were interested in obtaining genetic testing for their child. This research was important because it identified actionable barriers including insurance coverage, cost, uncertainty of how to attain testing, and more pressing health concerns for their child. Future research may explore a possible lack of accessibility to genetic services for some families within this population based on these results. Additionally, knowledge of these barriers can promote further studies and potentially the implementation of strategies to improve the financial coverage for genetic testing and streamline the genetic testing process for pediatric HCM patients.

4.2 RESEARCH SIGNIFICANCE TO GENETIC COUNSELING

Genetic counselors play a significant role in educating families of pediatric patients with HCM and facilitating the genetic testing process. In addition to the data collected regarding the barriers to genetic testing in this patient population, a deficit in patient understanding regarding the utility and issues associated with genetic testing is suggested by this research. Therefore, there is a need to further educate patients regarding what genetic testing is and the information that it provides. A Genetic Counseling Practice-Based Competency as established by ACGC states that genetic counselors, “effectively educate clients about a wide range of genetics and genomics information based on their needs, their characteristics and the circumstances of the encounter” (Doyle et al., 2016). One of the study findings indicates that participants, specifically those who

had already pursued testing for their child, felt that the genetic test was uninformative because their child was already diagnosed with HCM. Additionally, the survey data indicated the possible need for additional education in certain areas such as GINA. Thus, these issues should be allotted more time for discussion. Additionally, distribution of educational resources focusing on the information that genetic testing provides as well as legal significance associated with the testing should be considered to reinforce parents' understanding regarding the implications of this testing for their child and family. Future research can continue to delineate specifics regarding the appropriate timing for this information, including the timing of the discussion regarding genetic testing and distribution of educational resources (e.g., when the child is diagnosed versus at a follow-up appointment when the family has had some time to process the diagnosis).

Ensuring that pediatric HCM patients and their families have access to genetic testing, as well as the understanding to make an informed decision regarding genetic testing and an appreciation for what a genetic result will mean for the patient's family demonstrates the importance of this research study to the genetic counseling and public health fields. This research highlights a need for genetic counselors in a cardiovascular clinic. Additionally, this study demonstrates a need to offer genetic testing as a standard of clinical care for individuals with HCM. While it is ultimately the patient's decision regarding whether or not they pursue genetic testing, this research suggests that many families may depend on their healthcare provider, insurance coverage, and additional factors that were not assessed within the scope of this study. Overall, this research has the potential to impact not only clinical practice in the Cardiovascular Genetics Clinic at UPMC Children's Hospital of Pittsburgh but could ultimately impact the approach to patient care in other cardiovascular genetics clinics.

APPENDIX A UNIVERSITY OF PITTSBURGH IRB APPROVAL LETTER

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
<http://www.irb.pitt.edu>

Memorandum

To: Mousumi Moulik
From: IRB Office
Date: 9/27/2018
IRB#: [PRO18050725](#)
Subject: Barriers to Uptake of Genetics Services in Families of Pediatric Hypertrophic
Cardiomyopathy Patients

The University of Pittsburgh Institutional Review Board reviewed and approved the above referenced study by the expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110. Your research study was approved under:

The IRB has approved the waiver for the requirement to obtain a written informed consent.

The IRB has approved the waiver for the requirement to obtain informed consent to use protected health information to identify potential research subjects.






The risk level designation is Minimal Risk.

Approval Date: 9/27/2018
Expiration Date: 9/26/2019

For studies being conducted in UPMC facilities, no clinical activities can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

APPENDIX B STUDY SURVEY

Survey Flow Barriers to Uptake of Genetic Services in Families of Pediatric Hypertrophic Cardiomyopathy Patients

→	 Show Block: Intro and Consent (1 Question)	Add Below	Move	Duplicate	Delete
→	 Show Block: General Diagnosis and Family History (13 Questions)	Add Below	Move	Duplicate	Delete
→	 Show Block: Genetic Evaluation (11 Questions)	Add Below	Move	Duplicate	Delete
→	 Show Block: Attitudes Toward Genetic Testing (6 Questions)	Add Below	Move	Duplicate	Delete
→	 Show Block: Demographics (11 Questions)	Add Below	Move	Duplicate	Delete

Start of Block: Intro and Consent

Q1 If you are the parent or guardian of a child who has been diagnosed with hypertrophic cardiomyopathy... You are invited to participate in a research study called, "Barriers to Uptake of Genetic Services in Families of Pediatric Hypertrophic Cardiomyopathy Patients." My name is Rebecca Clark, and I am a genetic counseling graduate student at the University of Pittsburgh. I am conducting this research as part of my training and have worked with the Department of Cardiology at UPMC Children's Hospital of Pittsburgh to reach you. While working at Children's Hospital, I have become interested in why some families of children with HCM pursue genetic testing while others do not. The purpose of this study is to determine the difficulties families of children with HCM may face in receiving genetic testing. I hope to publish the results of this study in a medical journal, so doctors and other healthcare providers can better understand the experiences and healthcare needs of families with HCM. In order to participate in this study, I have developed a survey for you to fill out that will take about 20 to 30 minutes to complete. You may save your progress and return to the survey later if you use the same computer to complete it. The survey will ask some brief questions regarding your child's diagnosis of HCM, experiences with genetic testing, and some background information (i.e., child's gender, age, etc.). Your responses will remain confidential and will be stored on secure computers in offices that require key-card access at UPMC Children's Hospital of Pittsburgh. Also, the information you provide will be anonymous and cannot be linked to you, your child, or your family. There are no direct benefits to participating in this study. There is no cost to participate in this study. Risks associated with participating in this study are limited but can include negative feelings brought on by answering questions regarding difficult or stressful situations, including your child's diagnosis and its impact on your family. Participation in this study is voluntary, and you may withdraw from the study at any time. If you have any questions or concerns about this study, please contact Rebecca Clark at 412-692-7565 or rebecca.clark8@chp.edu. Thank you for participating, and I look forward to using this project to help build knowledge about genetic testing for HCM to improve the care provided to individuals and families with HCM.

- ☐ I would like to take the survey. (1)
- ☐ I would not like to take the survey. (2)

Skip To: End of Survey if you are the parent or guardian of a child who has been diagnosed with hypertrophic cardiomyopa... = I would not like to take the survey.

End of Block: Intro and Consent

Start of Block: General Diagnosis and Family History

Q2 Do you have at least one child who has been diagnosed with hypertrophic cardiomyopathy?

☐ Yes (1)

☐ No (2)

Skip To: End of Survey If Do you have at least one child who has been diagnosed with hypertrophic cardiomyopathy? = No

Q3 Do you have other children?

☐ Yes (1)

☐ No, and I am not planning on having more children (2)

☐ No, but I am planning on having more children (3)

Display This Question:

If Do you have other children? = Yes

Q4 Are your other children affected with hypertrophic cardiomyopathy?

☐ Yes (1)

☐ No (2)

Q5 How old was your child when he/she was diagnosed? (If you have more than 1 child who is diagnosed with HCM, please provide this and future responses in reference to your MOST RECENTLY diagnosed child.)

Q6 Why was your child originally referred to be evaluated for hypertrophic cardiomyopathy?
(Please check all that apply)

- ☐ Family history – cardiac (heart) evaluation was done (1)
 - ☐ Family history – genetic testing was done (2)
 - ☐ Child was having symptoms (dizziness, chest pain, fainting, palpitations, shortness of breath, other) (3)
 - ☐ A murmur or heart problem was detected upon routine checkup (4)
 - ☐ Other (5) _____
-

Q7 Do you think you are at risk for developing hypertrophic cardiomyopathy, based on your child's diagnosis?

- ☐ Yes (1)
 - ☐ No (2)
 - ☐ I don't know (3)
 - ☐ N/A - I was diagnosed before my child (4)
-

Q8 Have you been screened for hypertrophic cardiomyopathy? (Please check all that apply.)

- ☐ Yes, I saw a cardiologist (heart doctor) (1)
 - ☐ Yes, I had an echocardiogram (also known as an Echo, which is a heart ultrasound) (2)
 - ☐ Yes, I had an electrocardiogram (also known as ECG or EKG, which involves putting sensors on your chest and measures the heart's rhythm) (3)
 - ☐ Yes, I had a heart MRI (This is a test that takes 30 to 90 minutes and involves lying on a bed and entering into a machine where pictures of your heart are taken.) (4)
 - ☐ Yes, I had a Holter monitor (a small, wearable device that you wear for about 24 hours that checks your heart rhythm) (5)
 - ☐ Yes, I had genetic testing (6)
 - ☐ Yes, I had other screening – please describe (7) _____
 - ☐ No, I have not been screened at this time (8)
-

Q9 Have you been counseled by a healthcare provider regarding how the chance of developing hypertrophic cardiomyopathy can be passed down through a family?

- ☐ Yes (1)
 - ☐ No (2)
 - ☐ I don't know (3)
-

Display This Question:

If Have you been counseled by a healthcare provider regarding how the chance of developing hypertrop... = Yes

Q10 Who counseled you regarding your chance of developing HCM? (Please check all that apply.)

- ☐ Cardiologist (heart doctor) (1)
- ☐ Primary care physician/pediatrician (2)
- ☐ Nurse practitioner/physician assistant (3)
- ☐ Genetic counselor (4)
- ☐ Geneticist (5)
- ☐ Other (6) _____
- ☐ I don't know (7)

Q11 Have any of your child's blood relatives (siblings, parents, grandparents, aunts, uncles, or cousins) been diagnosed with hypertrophic cardiomyopathy?

- ☐ Yes (1)
- ☐ No (2)
- ☐ I don't know (3)

Skip To: Q14 If Have any of your child's blood relatives (siblings, parents, grandparents, aunts, uncles, or cous... != Yes

Q12 Who was diagnosed (relationship to your child)? (Please check all that apply)

- ☐ Sibling(s) (brother/sister) (1)
 - ☐ Parent (mother/father) (2)
 - ☐ Grandparent(s) (3)
 - ☐ Aunt(s)/uncle(s) (4)
 - ☐ Cousin(s) (5)
 - ☐ Other (6) _____
-

Q13 How many people, other than your child, in the family have hypertrophic cardiomyopathy?
(Okay to estimate)

Q14 Have there been any instances of sudden cardiac arrest in the family? (This may include but is not limited to a heart attack, an unexplained accident, or good swimmer drowning.)

- ☐ Yes (1)
- ☐ No (2)
- ☐ I don't know (3)

End of Block: General Diagnosis and Family History

Start of Block: Genetic Evaluation

Q15 Has your child ever had genetic testing for hypertrophic cardiomyopathy?

- ☐ Yes (1)
- ☐ No (2)

Skip To: Q22 If Has your child ever had genetic testing for hypertrophic cardiomyopathy? = No

Q16 Did you request the genetic test or did a medical professional that your child sees for hypertrophic cardiomyopathy recommend it for him/her?

- ☐ I requested it. (1)
- ☐ Child's healthcare provider recommended it. (2)
- ☐ I asked about genetic testing, and it was recommended as well. (3)

Q17 Who does your child see for hypertrophic cardiomyopathy? (Please check all that apply)

- ☐ Cardiologist (heart doctor) (1)
- ☐ Primary care physician/pediatrician (2)
- ☐ Nurse practitioner/physician assistant (3)
- ☐ Genetic counselor (4)
- ☐ Geneticist (5)
- ☐ Other (6) _____
- ☐ Unknown (7)

Q18 What were the findings of the genetic test?

- ☐ A known disease-causing mutation (A change in a gene that causes hypertrophic cardiomyopathy was identified.) (1)
- ☐ A variant of uncertain significance (A change in a gene was identified, but its effects cannot be determined.) (2)
- ☐ No mutation or variant was identified (No change in a gene was identified.) (3)
- ☐ I am not sure (4)
-

Q19 Who have you discussed the genetic testing with? (Please check all that apply)

- ☐ Family (1)
- ☐ Friends (2)
- ☐ Genetics professional (a genetic counselor or geneticist) (3)
- ☐ Cardiologist (4)
- ☐ Your child's primary care physician (5)
- ☐ Other (6) _____
-

Q20 In what ways, if any, was your child's genetic testing valuable?

Q21 In what ways, if any, was your child's genetic testing not valuable?

Skip To: End of Block If In what ways, if any, was your child's genetic testing not valuable? Is Displayed

Q22 Are you interested in pursuing genetic testing for your child for hypertrophic cardiomyopathy in the future?

- ☐ Yes (1)
 - ☐ No (2)
 - ☐ Not sure (3)
-

Q23 Who does your child see for hypertrophic cardiomyopathy? (Please check all that apply)

- ☐ Cardiologist (heart doctor) (1)
 - ☐ Primary care physician/pediatrician (2)
 - ☐ Nurse practitioner/physician assistant (3)
 - ☐ Genetic counselor (4)
 - ☐ Geneticist (5)
 - ☐ Other (6) _____
 - ☐ Unknown (7)
-

Q24 What is/are the main reason(s) for not obtaining genetic testing for your child? (Please check all that apply)

- ☐ Not interested (1)
 - ☐ Interested, but not sure how to pursue (2)
 - ☐ Interested, but not a priority for my child's healthcare at this time (i.e., due to time constraints and/or more pressing medical issues) (3)
 - ☐ Interested, but not offered testing by cardiologist or other medical professional (4)
 - ☐ Interested, but genetic testing is too expensive (5)
 - ☐ Interested, but genetic testing was denied by insurance (6)
 - ☐ Interested, but the process to receive genetic testing is too long (7)
 - ☐ Interested, but not provided a referral to Medical Genetics for genetic testing (8)
 - ☐ Interested, but the waitlist to see Medical Genetics was too long (9)
 - ☐ Other (10) _____
-

Q25 Is there anything you would like to know before making your decision about pursuing genetic testing for your child?

End of Block: Genetic Evaluation

Start of Block: Attitudes Toward Genetic Testing

Q26 In your opinion, what are the main benefits of genetic testing? (Please check all that apply.)

- ☐ Identifying family members at risk to develop HCM (1)
 - ☐ Contributing to genetic information and/or research (2)
 - ☐ Helping to direct care of my child for HCM (3)
 - ☐ Providing a more complete understanding of my child's HCM diagnosis (4)
 - ☐ Relief, from gaining knowledge and potentially having a definitive answer (5)
 - ☐ I don't know (6)
 - ☐ Other (7) _____
-

Q27 In your opinion, what are the main risks of genetic testing? (Please check all that apply.)

- ☐ Time-consuming, lengthy process (1)
 - ☐ Financial cost (2)
 - ☐ Incidental findings (i.e., Genetic tests can potentially reveal health concerns and/or risks for a disease for my child that we do not want to know.) (3)
 - ☐ Anxiety and distress, from waiting for the result and/or its implications for my child and our family (4)
 - ☐ Possible future discrimination by employers and/or insurance (5)
 - ☐ I don't know (6)
 - ☐ Other (7) _____
-

Display This Question:

If Has your child ever had genetic testing for hypertrophic cardiomyopathy? = Yes

Q28 Please respond to these statements.

	Strongly agree (1)	Somewhat agree (2)	Neither agree nor disagree (3)	Somewhat disagree (4)	Strongly disagree (5)	N/A (6)
I pursued genetic testing for my child because my healthcare provider advised me to. (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Requests from my family members encouraged me to pursue genetic testing for my child. (2)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I pursued genetic testing for my child to learn about the risks for myself. (3)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I pursued genetic testing for my child to learn about the risks for my other children (if applicable). (4)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I pursued genetic testing for my child to learn about the risks for my other family members. (5)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Health insurance coverage was a factor in my child getting genetic testing for hypertrophic cardiomyopathy. (6)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Genetic testing was accessible to my child and my family. (7)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I was hesitant to pursue genetic testing for my child because of the possible negative impact	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

on myself and other family members. (8)

GINA (the Genetic Information Non-discrimination Act) is a law that was passed in 2008 that makes sure health insurance companies will not deny coverage and employers cannot make hiring/firing decisions based on genetic testing results. GINA will protect my child from future discrimination and unlawful termination of employment and ensure their access to health insurance. (9)



Display This Question:

If Has your child ever had genetic testing for hypertrophic cardiomyopathy? = Yes

Q29 The information gained from my child having a genetic test for hypertrophic cardiomyopathy:

	Strongly agree (1)	Somewhat agree (2)	Neither agree nor disagree (3)	Somewhat disagree (4)	Strongly disagree (5)	N/A (6)
Encouraged our family to take action towards a healthier lifestyle to prevent symptoms of hypertrophic cardiomyopathy (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Helped our family make better decisions regarding healthcare (2)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Made me concerned about my child's, my own, and/or other family members' future health insurance coverage (3)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Caused a lot of anxiety and distress (4)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Caused relief to know my child's genetic status (5)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Was not helpful because my child was already diagnosed with hypertrophic cardiomyopathy through a cardiac evaluation (6)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Display This Question:

If Has your child ever had genetic testing for hypertrophic cardiomyopathy? = No

Q30 Please respond to these statements.

	Strongly agree (1)	Somewhat agree (2)	Neither agree nor disagree (3)	Somewhat disagree (4)	Strongly disagree (5)	N/A (6)
I would pursue genetic testing for my child if my healthcare professional advised me to. (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Requests from my family members would make me more likely to pursue genetic testing for my child. (2)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I would pursue genetic testing for my child to learn about the risks for myself. (3)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I would pursue genetic testing for my child to learn about the risks for my other children (if applicable). (4)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I would pursue genetic testing for my child to learn about the risks for my other family members. (5)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Health insurance coverage would be a factor in my child getting genetic testing for hypertrophic cardiomyopathy. (6)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I believe my child would have access to genetic testing if I wanted to pursue it. (7)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

I would prefer my child not get genetic testing because of the possible negative impact on myself and other family members. (8)



GINA (the Genetic Information Non-discrimination Act) is a law that was passed in 2008 that makes sure health insurance companies will not deny coverage and employers cannot make hiring/firing decisions based on genetic testing results. GINA will protect my child from future discrimination and unlawful termination of employment and ensure their access to health insurance. (9)



Display This Question:

If Has your child ever had genetic testing for hypertrophic cardiomyopathy? = No

Q31 The information gained from my child having a genetic test for hypertrophic cardiomyopathy would:

	Strongly agree (1)	Somewhat agree (2)	Neither agree nor disagree (3)	Somewhat disagree (4)	Strongly disagree (5)	N/A (6)
Encourage our family to take action towards a healthier lifestyle to prevent symptoms of hypertrophic cardiomyopathy (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Help our family make better decisions regarding healthcare (2)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Make me concerned about my child's, my own, and/or other family members' future health insurance coverage (3)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Cause a lot of anxiety and distress (4)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Cause relief (5)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Is not helpful because my child can be diagnosed with hypertrophic cardiomyopathy through a cardiac evaluation (6)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

End of Block: Attitudes Toward Genetic Testing

Start of Block: Demographics

Q32 What is your child's age currently?

Q33 What is your child's gender?

☐ Male (1)

☐ Female (2)

Q34 What is your child's race/ethnicity? (Please check all that apply.)

☐ White (1)

☐ Black or African American (2)

☐ American Indian or Alaska Native (3)

☐ Asian (4)

☐ Native Hawaiian or Pacific Islander (5)

☐ Other (6) _____

Q35 Does your child have health insurance coverage?

☐ Yes (1)

☐ No (2)

☐ I don't know (3)

Display This Question:

If Does your child have health insurance coverage? = Yes

Q36 Does your child have:

- ☐ Private insurance (includes UPMC, Cigna, Highmark, Aetna, United Healthcare) (1)
 - ☐ Medicaid, also known as CHIP (includes UPMC for You, Gateway, United Healthcare for Families, and Aetna Better Health) (2)
 - ☐ I don't know (3)
-

Q37 What is your family's home community

- ☐ Urban (1)
 - ☐ Suburban (2)
 - ☐ Rural (3)
 - ☐ I don't know (4)
-

Q38 How far away do you live from UPMC Children's Hospital of Pittsburgh?

- ☐ 30 minutes or less (1)
 - ☐ Between 30 minutes and 1 hour (2)
 - ☐ Between 1 hour and 2 hours (3)
 - ☐ Between 2 hours and 3 hours (4)
 - ☐ 3 hours or more (5)
-

Q39 What is the highest level of education obtained by someone in your household?

- ☐ Less than high school degree (1)
 - ☐ High school graduate (high school diploma or equivalent including GED) (2)
 - ☐ Some college but no degree (3)
 - ☐ Associate degree in college (2-year) (4)
 - ☐ Bachelor's degree in college (4-year) (5)
 - ☐ Master's degree (6)
 - ☐ Doctoral degree (7)
 - ☐ Professional degree (JD, MD) (8)
-

Q40 Does someone in your household work in the healthcare or medical field?

- ☐ Yes (1)
 - ☐ No (2)
-

Q41 How are you related to your child with HCM?

- ☐ Mother (1)
 - ☐ Father (2)
 - ☐ Other - please describe (3) _____
-

Q42 Please indicate if your child is adopted or in foster care.

- ☐ Yes, adopted (1)
- ☐ Yes, in foster care (2)
- ☐ No (3)

End of Block: Demographics

APPENDIX C RECRUITMENT LETTER

To the parent or guardian of

My name is Dr. Mousumi Moulik, and I am a member of the clinical team in the Department of Cardiology at UPMC Children's Hospital of Pittsburgh. I am writing to invite you to participate in a research study about the barriers to genetic testing in families of children with hypertrophic cardiomyopathy (HCM). This research study is being conducted by Rebecca Clark, a genetic counseling student who is currently studying at the University of Pittsburgh. She is conducting this research as part of her training and has worked with the Department of Cardiology to reach you all. You are eligible to be in this study because your child was seen by our clinical team for a diagnosis of hypertrophic cardiomyopathy (HCM).

Participation involves completing an online survey. If you'd like to participate, simply type in the link below on a computer to fill out a survey that Rebecca developed, which should take about 20-30 minutes to complete. This research is trying to understand why some families choose to have genetic testing and why some families do not.

The link for the survey is below:

https://pitt.co1.qualtrics.com/jfe/form/SV_9LJDXWvsOGIdcRn

If you provided your email address to us here at UPMC, Rebecca will be following up to this letter with an email that further explains the survey and contains the survey link.

If you have any questions or concerns about the study, please contact Rebecca Clark at 412-692-7565 or by email at rebecca.clark8@chp.edu. Thank you very much for considering participation. We look forward to using this project to help build knowledge on genetic testing in families with HCM and improve the care provided to your child and family.

Sincerely,

Dr. Mousumi Moulik
Assistant Professor, Pediatrics (Cardiology), University of Pittsburgh School of Medicine
Director, Pediatric Cardiovascular Genetics Clinic, UPMC Children's Hospital of Pittsburgh

APPENDIX D EMAIL REMINDERS

D.1 First Reminder

Good morning,

My name is Rebecca Clark, and I am a genetic counseling student at the University of Pittsburgh. I am writing to invite you to participate in a research study that I am conducting as part of my training about the barriers to genetic testing in families of children with hypertrophic cardiomyopathy. I am following up on a letter that you should have received from Dr. Mousumi Moulik from the Department of Cardiology at UPMC Children's Hospital of Pittsburgh.

Participation involves completing an online survey. If you'd like to participate, simply click the link below to fill out a survey that I developed, which should take about 20-30 minutes to complete. This research is trying to understand why some families choose to have genetic testing and why some families do not.

The link for the survey is below:

https://pitt.co1.qualtrics.com/jfe/form/SV_9LJDXWvsOGldcRn

If you already completed the survey using the survey link in the letter, please disregard this email and do not fill out the survey again.

If you have any questions or concerns about the study, please contact Rebecca Clark at 412-692-7565 or by email at rebecca.clark8@chp.edu. Thank you very much for considering participation. We look forward to using this project to help build knowledge on genetic testing in families with HCM and improve the care provided to your child and family.

Best,
Rebecca

D.2 Second Reminder

Good afternoon,

My name is Rebecca Clark, and I am emailing you as a reminder to participate in a research study that I am conducting about the barriers to genetic testing in families of children with hypertrophic cardiomyopathy.

Participation involves completing an online survey. If you'd like to participate, simply click the link below to fill out a survey that I developed, which should take about 20-30 minutes to complete. This research is trying to understand why some families choose to have genetic testing and why some families do not.

The link for the survey is below:

https://pitt.co1.qualtrics.com/jfe/form/SV_9LJDXWvsOGIdcRn

If you already previously completed the survey, please disregard this email and do not fill out the survey again.

If you have any questions or concerns about the study, please contact Rebecca Clark at 412-692-7565 or by email at rebecca.clark8@chp.edu. Thank you very much for considering participation. We look forward to using this project to help build knowledge on genetic testing in families with HCM and improve the care provided to your child and family.

Best,
Rebecca

APPENDIX E SUPPLEMENTAL DATA

Table 7 Supplemental Demographic Data

Variable	+Genetic Testing	-Genetic Testing	Total
What is your family's home community?			
Urban	16.7% (1)	0% (0)	9.1% (1)
Suburban	33.3% (2)	40.0% (2)	36.4% (4)
Rural	50.0% (3)	60.0% (3)	54.5% (6)
How far away do you live from UPMC Children's Hospital of Pittsburgh?			
30 minutes or less	16.7% (1)	0% (0)	9.1% (1)
Between 30 minutes and 1 hour	33.3% (2)	40.0% (2)	36.4% (4)
Between 1 hour and 2 hours	16.7% (1)	20.0% (1)	18.2% (2)
Between 2 hours and 3 hours	16.7% (1)	20.0% (1)	18.2% (2)
3 hours or more	16.7% (1)	20.0% (1)	18.2% (2)
What is the highest level of education obtained by someone in your household?			
High school graduate (high school diploma or equivalent including GED)	16.7% (1)	0% (0)	9.1% (1)
Some college but no degree	16.7% (1)	40.0% (2)	27.3% (3)
Associate degree in college (2-year)	16.7% (1)	0% (0)	9.1% (1)
Bachelor's degree in college (4-year)	16.7% (1)	40.0% (2)	27.3% (3)
Master's degree	16.7% (1)	20.0% (1)	18.2% (2)
Professional degree (JD, MD)	16.7% (1)	0% (0)	9.1% (1)
Does someone in your household work in the healthcare or medical field?			
Yes	66.7% (4)	60.0% (3)	63.6% (7)

Table 7 Continued

No	33.3% (2)	40.0% (2)	36.4% (4)
How are you related to your child with HCM?			
Mother	83.3% (5)	80.0% (4)	81.8% (9)
Father	16.7% (1)	0% (0)	9.1% (1)
Other*	0% (0)	20.0% (1)	9.1% (1)

*Grandmother

Table 8 Attitudes of + Genetic Testing Respondents

	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree	N/A
I pursued genetic testing for my child because my healthcare provider advised me to.	5 (83.3%)	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Requests from my family members encouraged me to pursue genetic testing for my child.	1 (16.7%)	1 (16.7%)	1 (16.7%)	0 (0%)	2 (33.3%)	1 (16.7%)
I pursued genetic testing for my child to learn about the risks for myself.	4 (66.7%)	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)	1 (16.7%)
I pursued genetic testing for my child to learn about the risks for my other children (if applicable).	6 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
I pursued genetic testing for my child to learn about the risks for my other family members.	4 (66.7%)	2 (33.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Health insurance coverage was a factor in my child getting genetic testing for hypertrophic cardiomyopathy.	3 (50.0%)	1 (16.7%)	1 (16.7%)	0 (0%)	1 (16.7%)	0 (0%)
Genetic testing was accessible to my child and my family.	3 (50.0%)	2 (33.3%)	0 (0%)	0 (0%)	1 (16.7%)	0 (0%)
I was hesitant to pursue genetic testing for my child because of the possible negative impact on myself and other family members.	0 (0%)	1 (16.7%)	0 (0%)	1 (16.7%)	4 (66.7%)	0 (0%)
GINA (the Genetic Information Non-discrimination Act) is a law that was passed in 2008 that makes sure health insurance companies will not deny coverage and employers cannot	1 (20.0%)	0 (0%)	3 (60.0%)	0 (0%)	1 (20.0%)	0 (0%)

Table 8 Continued

make hiring/firing decisions based on genetic testing results. GINA will protect my child from future discrimination and unlawful termination of employment and ensure their access to health insurance.						
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Table 9 Attitudes of -Genetic Testing Respondents

	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree	N/A
I would pursue genetic testing for my child if my healthcare professional advised me to.	1 (20%)	2 (40%)	2 (40%)	0 (0%)	0 (0%)	0 (0%)
Requests from my family members would make me more likely to pursue genetic testing for my child.	0 (0%)	3 (60%)	2 (40%)	0 (0%)	0 (0%)	0 (0%)
I would pursue genetic testing for my child to learn about the risks for myself.	0 (0%)	2 (40%)	1 (20%)	1 (20%)	0 (0%)	1 (20%)
I would pursue genetic testing for my child to learn about the risks for my other children (if applicable).	2 (40%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	2 (40%)
I would pursue genetic testing for my child to learn about the risks for my other family members.	1 (20%)	2 (40%)	1 (20%)	1 (20%)	0 (0%)	0 (0%)
Health insurance coverage would be a factor in my child getting genetic testing for hypertrophic cardiomyopathy.	4 (80%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)
I believe my child would have access to genetic testing if I wanted to pursue it.	1 (20%)	2 (40%)	1 (20%)	0 (0%)	1 (20%)	0 (0%)
I would prefer my child not get genetic testing because of the possible negative impact on myself and other family members.	0 (0%)	0 (0%)	0 (0%)	1 (20%)	4 (80%)	0 (0%)
GINA (the Genetic Information Non-discrimination Act) is a law that was passed in 2008 that makes sure health insurance companies will not deny coverage and employers cannot make hiring/firing decisions based on genetic testing results. GINA will protect my child from future discrimination and unlawful termination of employment and ensure their access to health insurance.	0 (0%)	2 (40%)	2 (40%)	0 (0%)	1 (20%)	0 (0%)

Table 10 +Genetic Test Perception of Information

	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree	N/A
Encouraged our family to take action towards a healthier lifestyle to prevent symptoms of hypertrophic cardiomyopathy	2 (33.3%)	3 (50.0%)	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)
Helped our family make better decisions regarding healthcare	2 (33.3%)	3 (50.0%)	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)
Made me concerned about my child's, my own, and/or other family members' future health insurance coverage	3 (50.0%)	0 (0%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	0 (0%)
Caused a lot of anxiety and distress	1 (16.7%)	3 (50.0%)	1 (16.7%)	0 (0%)	1 (16.7%)	0 (0%)
Caused relief to know my child's genetic status	3 (50.0%)	2 (33.3%)	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)
Was not helpful because my child was already diagnosed with hypertrophic cardiomyopathy through a cardiac evaluation	2 (33.3%)	1 (16.7%)	3 (50.0%)	0 (0%)	0 (0%)	0 (0%)

Table 11 -Genetic Test Perception of Information

	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree	N/A
Encourage our family to take action towards a healthier lifestyle to prevent symptoms of hypertrophic cardiomyopathy	3 (60.0%)	2 (40.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Help our family make better decisions regarding healthcare	3 (60.0%)	2 (40.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Make me concerned about my child's, my own, and/or other family members' future health insurance coverage	1 (20.0%)	3 (60.0%)	1 (20.0%)	0 (0%)	0 (0%)	0 (0%)
Cause a lot of anxiety and distress	0 (0%)	0 (0%)	3 (60.0%)	0 (0%)	1 (20.0%)	1 (20.0%)
Cause relief	1 (20.0%)	3 (60.0%)	1 (20.0%)	0 (0%)	0 (0%)	0 (0%)
Is not helpful because my child can be diagnosed with hypertrophic cardiomyopathy through a cardiac evaluation	1 (20.0%)	2 (40.0%)	2 (40.0%)	1 (20.0%)	0 (0%)	0 (0%)

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